AUTONOMIC FUNCTION IN EPILEPSY

Dr PATRICK ADJEI BSc MB CHB MWACP MSc

UNIVERSITY COLLEGE LONDON

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Declaration

I, DR PATRICK ADJEI declare and confirm that the work presented in this thesis is my own. All of the work is original and where information has been derived from other sources, I confirm that I have indicated this in the thesis.

Signed: 

Date: 19th January 2011

Abstract

Autonomic function may help to localize and manage the epilepsies. It is likely that the mechanisms of Sudden Unexpected death in Epilepsy (SUDEP) involve autonomic disturbance and a better understanding of these might lead to measures that would help reduce the mortality in patients afflicted with epilepsy. In this thesis, I first provide a comprehensive literature review of the association between epilepsy and the autonomic nervous system. I then evaluate heart rate variability and other cardiac and endocrine parameters as indices of cardiac autonomic function to test three hypothesis; 1) Changes in heart rate variability (HRV), can occur in the peri-ictal period during both (a) subclinical electrographic seizures and (b) clinically overt partial seizures, and can help to localise and lateralise the ictal discharge. 2) Intractable epilepsy can disrupt the heart rate variability and its circadian rhythm. 3) Epileptic seizures affect the serum concentration of the catecholamines and the electrolytes and that these changes could impact on the corrected QT interval. Subjects (n=207) with intractable epilepsy who were being evaluated with video-EEG telemetry for epilepsy surgery were recruited for this study.

I found that subclinical seizures have no effect on the HRV. However, in overt partial seizures, HRV decreases, corrected QT is prolonged and plasma catecholamines increases. The reduction in HRV during seizures is not affected by the hemispheric or lobar location of the epileptic focus. However, in the interictal period, reduced HRV differs in left vs. right hemisphere, and in temporal vs. extratemporal areas. The diurnal pattern of HRV is not altered in epilepsy and the mean day HRV were significantly different from mean night HRV. The reduction in HRV is also associated with the following clinical factors: prolonged medical history of epilepsy, the cortical pathology itself, the nature of the seizures, higher seizure frequency and the antiepileptic drug treatment. The plasma electrolytes: Na, K^{+}, Ca^{2+} and cardiac troponin are not affected after a seizure. However, plasma Mg^{2+} was seen to increase after a seizure. These abnormalities in autonomic control, particularly the reduction in HRV might be one contributory mechanism of Sudden Unexpected Death in Epilepsy (SUDEP).

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Glossary of Abbreviations

AD	Adrenaline
ANS	Autonomic nervous system
AAD	Average absolute difference
ASCII	American Standard Code for Information Interchange
BP	Blood pressure
BPM	Beats per minute (unit of heart rate)
CAN	Central autonomic network
CD	Compact Disc
DDDR	Dual chambers paced, Dual chamber sensed, Dual response to sensing, Rate modulation (Generic code for antibradycardia pacing)
DSM	Diagnostic and Statistical Manual of Diseases
ECG	Electrocardiograph
EDF	European Data Format
EEG	Electroencephalograph
FLE	Frontal lobe epilepsy
GI	Gastrointestinal
HF	High frequency power
HFF	High Frequency Filter
HR	Heart rate
HRV	Heart rate variability
ICD	International Classification of Diseases
LTM	Long Term Monitoring
LF	Low frequency power
LFF	Low Frequency Filter
MHR	Mean instantaneous heart rate
Mmol/l	Millimoles per litre
MRI	Magnetic resonance imaging
NA	Noradrenalin
NK	Natural Killer cells
NN	Normal to Normal RR wave intervals
NTS	Nucleus of the Tractus Solitarus
OLE	Occipital lobe epilepsy
PET	Positron emission chromatography
Pg/ml	Picograms/millilitre
PLE	Parietal lobe epilepsy
RMSSD	Square root of the mean squared standard deviation
S/secs	seconds
SD	Standard deviation
SDNN	Standard deviation of the normal to normal RR intervals
SSR	Sympathetic skin response
SUDEP	Sudden unexplained death in epilepsy

SPECT	Single photon emission computed tomography
TINN	Triangular interpolation of normal to normal RR Intervals
TLE	Temporal lobe epilepsy
VLM	Ventolateral nucleus of the Medulla

Acknowledgement

“I forget what I was taught. I only remember what I learned”, as said by Patrick White, Nobel Prize winner for literature in 1973. All that is written in here are the results of 36 months of self directed learning.

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Chapter 1

Aims

The general basis for this study is that in epilepsy significant changes occur in body physiology particularly the cardiovascular system, as a result of the activation of the autonomic nervous system. In this thesis, I studied a number of aspects of autonomic function ictally and interictally, to elucidate the nature and extent of the perturbation caused by epilepsy. The aims of the work were as follows:

1. To provide a comprehensive literature review of the links between epilepsy and the autonomic nervous system (both the effects of epilepsy on the autonomic nervous system and the effects of the autonomic nervous system on epilepsy).

2. To test three hypotheses:
    - Changes in heart rate variability (HRV), as an index of autonomic function can occur in the peri-ictal period during: (a) Subclinical electrographic seizures, (b) Clinically overt complex partial seizures, and can help to localise and lateralise the ictal discharge.

    - Intractable epilepsy can disrupt the heart rate variability and its circadian rhythm.

    - Epileptic seizures affect the serum concentration of adrenalin and noradrenalin, and the electrolytes (sodium, calcium, magnesium and potassium) and that these changes could impact on the corrected QT interval.

Chapter 2

Literature Review: the links between epilepsy and the autonomic nervous system

The first aim of this thesis was to provide a comprehensive review of the autonomic aspects of epileptic seizures and of epilepsy. Epileptic seizures are recurrent paroxysmal and unprovoked episodes of abnormal brain cortex electrical activity and result in a range of clinical symptoms that includes abnormal autonomic phenomena, sensory phenomena, involuntary movements, altered levels of consciousness, abnormalities of behaviour and cognitive function. A wide range of autonomic features (some of which may be life threatening) occur during seizures and indeed some partial seizures are manifest only by autonomic symptoms or signs (Baumgartner et al. 2001; Panayiotopoulos 2007). These autonomic features are thought to be mediated by cortical discharges recruiting the central autonomic network, pathways (Devinsky et al. 1994). The clinical range and significance of autonomic dysfunction during seizures are not fully understood and in some cases have been misdiagnosed as a primary disorder of the target organ such as seizure associated arrhythmias (Freeman et al. 1995).

Autonomic changes during convulsive seizures have been studied, mainly in the artificial setting of electroconvulsive therapy and these studies have concentrated on the neurocardiac and neurorespiratory axis. In these studies, an initial fall in the blood pressure (BP) without compensatory rise in heart rate (HR) was observed; this was followed by a subsequent rise and fall of the (BP) and (HR), the latter persisting well into the post ictal period. At the same time there was respiratory arrest (Brown et al. 1973; Mosier et al. 1957). After these pioneering studies, several investigators in recent times, have linked varied autonomic responses to epilepsy (Druschky et al. 2001; Faustmann et al. 1994; Frysinger et al. 1993; Massetani et al. 1997; Tomson et al. 1998); one intriguing possibility is that the autonomic dysfunction in partial epilepsy may be lateralised and that its occurrence will therefore assist in cerebral lateralisation or localisation of seizures. Autonomic changes during seizures may have other implications. Sudden Unexplained Death in Epilepsy (SUDEP) is an important cause of death in epilepsy occurring in as many as one in a hundred patients per year in severe epilepsy (Sander et

al. 1996). The mechanisms underpinning SUDEP are unknown, but it is possible that autonomic dysfunction plays an important role. Patients with seizure related autonomic changes may be particularly at risk of SUDEP but this question has yet to be extensively investigated (Surges et al. 2009c). Heart rate variability (HRV) is a direct measure of autonomic influences on the heart. In non-epileptic patients, decreased HRV has been shown to be an independent predictor of cardiac arrhythmia and mortality, regardless of other risk factors (Ponikowski et al. 1996). While a large degree of variability is detrimental to efficient physiologic function too little variability is also pathological. HRV is a non invasive measure, that estimates the naturally occurring beat to beat variations in the heart rate; this is usually overlooked when the average heart rate is calculated (Kleiger et al. 2005). It is a useful method to evaluate the responsiveness and resilience of the heart. In most clinical applications, HRV is analysed by time and or frequency domain methods, the former is derived from measuring and calculating the differences in the normal to normal (NN) RR intervals and the latter involves spectral analysis of normal to normal RR interval series (Malik 1996). Autonomic cardiovascular function and cardiac excitability are substantially modulated by electrolytes such as potassium, calcium and magnesium as well as by direct modulation of stress hormones. These parameters can be modified during and after seizures.

An increase of potassium depresses the activity of the sinus node and leads to an increased excitability of ventricular myocytes due to a shift in the resting membrane potential. This increases the risk of ectopic cardiac excitation and arrhythmias. Moreover, a serum acidosis causes an increase in free calcium, leading to increased influx of calcium during cardiac action potentials, which could potentially lead to an increase in oxygen consumption. This seizure related changes in serum composition may favour the occurrence of threatening cardiac arrhythmias which possibly are linked to SUDEP. Also, cardiac injury related to seizures has been shown in some previous studies such as the occurrence of ST segment depression (Tigaran et al. 2003) and the presence of cardiac fibrosis in SUDEP patients (Natelson et al. 1998). In contrast to this, cardiac Troponin levels, a highly sensitive and specific biochemical marker of myocardial injury, remained unchanged following complex partial seizures in a small series of patients(Woodruff et al. 2003); cardiac muscle damage may however be more evident following tonic-clonic seizures. In addition to cardiac parameters, there are other

methods of measuring autonomic function. The autonomic skin response is a purely sympathetic phenomenon that remains lateralised to one side (Bannister et al. 1999)and it may be valuable in localising the seizure discharge focus in partial epilepsy. A variety of stimuli including electrical, can activate sweat glands cause production of sweat and a change in skin resistance in response to sympathetic cholinergic activation. There are limited studies on observations of the sympathetic skin response (SSR) in autonomic nervous system disorders (Bannister et al. 1988). Quantitative studies of skin resistance have methodological problems and poor sensitivity and specificity.

There is no doubt that any part of autonomic nervous system function, affecting many physiological systems can be affected during epilepsy and because of the presumed hemispheric specialization, certain autonomic symptoms could provide both lateralization and localization data in the seizure onset zone. A thorough search for paroxysmal autonomic abnormalities could contribute to the diagnosis and management for epilepsy, in fact the commonly occurring peri-ictal tachycardia led to the development of seizure detection algorithms that are used during epilepsy monitoring(O'Donovan et al. 1995), though these are not without errors.

So, why study autonomic functions in epilepsy? The rationale is two-fold. First, Autonomic function may help to localize, classify and manage the epilepsies accordingly; this research area has not been systematically explored. Second, it is likely that the mechanisms of SUDEP involve autonomic disturbance and a better understanding of these might lead to measures that would help reduce the mortality in patients afflicted with epilepsy.

2.1 Epilepsy

Epilepsy remains one of the oldest documented neurological conditions. It affects approximately 0.5-1% of the population. In the developed world, there are approximately 40-70/100000 people per year who develop epilepsy. There is a higher incidence in the developing world (100-190/100000 people per year). The incidence of epilepsy is higher in the low socioeconomic group, and this and the higher incidence of parasitic infections probably account for the higher incidence in the developing world (Sander 2007). A definition of epilepsy should be simple and precise (Panayiotopoulos 2007). Epilepsy is characterised by recurrent paroxysmal episodes of cerebral cortical dysfunction manifested by stereotyped alterations in behaviour. However, the response to a simple question, such as "what is epilepsy?" may differ from physician to physician, between patient and physician and even from patient to patient (Engel et al. 2008). In trying to come out with a unified concept for the definition of epilepsy, epileptic seizures and epilepsy have been defined separately. This separation is recognised by the international league against epilepsy (ILAE) which has definitions for both:

- Epileptic seizures are occurrence of transient signs and symptoms as a result of abnormal excessive and synchronous discharge of cortical neuronal activity.

- Epilepsy on the other is defined according to the ILAE commission as "A chronic condition of the brain characterised by an enduring propensity to generate and have epileptic seizures and by the neurobiological, cognitive, psychological and social consequences of this chronic condition.

These ILAE definitions are not without controversy as is seen in the comments (Ahmed 2005; Gomez-Alonso et al. 2005) related to the publication of the definitions (Fisher et al. 2005), but this is beyond the scope of this thesis. What is an essential feature of the definition is the emphasis on the presence of an intrinsic brain pathology (condition of the brain), which is still present (enduring propensity) even when seizures are not occurring (Engel et al. 2008). The neurobiological basis for epilepsy has been proposed to be: 1) alterations in cellular excitability, arising from abnormalities of mechanisms that affect membrane depolarisation and repolarisation, 2) a network defect, resulting

from abnormalities of neuronal integration and communication; such abnormal neuronal networks facilitates the aberrant generation and propagation of neuronal discharges. The clinical phenomenology of seizures in epilepsy results from the recruitment or dysfunction of distinct brain areas. These areas may be neighboring, but seizures can also propagate to distant brain areas including parts of the central autonomic network (CAN). The definitions for these brain regions in epilepsy are;

- Irritative zone; the cortical area that generates the interictal spike.
- Ictal onset zone; cortical area that generates ictal activity.
- Epileptogenic lesion is the structural abnormality of the brain responsible for the seizures
- Symptomatogenic zone is the region of the brain directly responsible for the first clinical symptoms.
- Functional deficit zone is the area of the cortex that exhibits deficits that are non epileptic in origin.
- And finally the epileptogenic zone which is the total region of the brain that must be removed to prevent seizure occurrence and symptomatology, and may include or overlap with all the above (Engel et al. 2008).

2.2 Epilepsy and the Autonomic Nervous System

The recruitment of the central autonomic network during seizure propagation is mediated by the extensive connections it has throughout the brain and brainstem and the presumed abnormality of neuronal networks in patients with epilepsy. Considering the extensive interconnection of the central autonomic network, it would be extremely surprising if widespread and localised abnormal and synchronised electrical discharge such as is seen in epilepsy occurred without some form of associated autonomic dysfunction. The dysfunction of autonomic nervous system associated with seizures, varies from subtle to gross alterations. In epilepsy, the signs of autonomic nervous system dysfunction are often overshadowed by the more apparent motor and higher cerebral effects of seizures, but autonomic disturbance is a common feature of many seizure types (Ansakorpi et al. 2000; Ansakorpi et al. 2002a). Altered autonomic activity in epilepsy has long been recognised and is mentioned in early texts. In an eighteenth

century (1769) text, there is a description of a priest whose epileptic seizures were always preceded by the onset of chest pain followed by nausea and vomiting (Uluc et al. 2004), and chest pain mimicking acute coronary syndromes have been observed in patients with epilepsy by Devinsky (Devinsky et al. 1986) and it was thought to be due to abnormal cardiac autonomic responses during seizures. Autonomic activity in epilepsy was recognised by Gower's but it was Wilder Penfield and colleagues who most thoroughly studied autonomic function by precipitating and observing autonomic symptoms through cortical electrical stimulation experiments (Penfield et al. 1957). Signs and symptoms attributable to the autonomic nervous system are present in the symptom complex of all generalized tonic- clonic seizures and most complex partial seizures and may occur as the only manifestation of a simple partial seizure, the majority of these being referred to the epigastrium (Wannamaker 1985).

When paroxysmal events predominantly cause recurrent stereotypical autonomic symptoms affecting the cardiovascular, respiratory, genitourinary, and digestive systems or pilomotor function of skin and integument and the pupillary sphincters, they are often referred to as autonomic seizures. These seizures have an ictal focus in the cortex that involves the central autonomic network. In other seizures the autonomic symptoms tend to occur in the post event or later in the ictal period (Goodman et al. 2008). Occasionally the symptom complex of a patient with epilepsy may include palpitations during the seizures (particularly during the aura) or peri-ictally and yet without evidence of ictal tachycardia. Whether these patients are describing a change in cardiac contractility or just an abnormal perception of stimuli remains unknown. The peripheral autonomic nervous system is under the influence of the cerebral neocortex through the integrated activity of the central autonomic network (Barron et al. 1993) and epilepsy has a variety of effects on the autonomic nervous system (Figure 1), during "Partial" and "Generalized" epilepsy and these responses which remain largely stereotypical in both epilepsy types, have a final common pathway for autonomic symptoms from the cerebral neocortex (Figure 2).

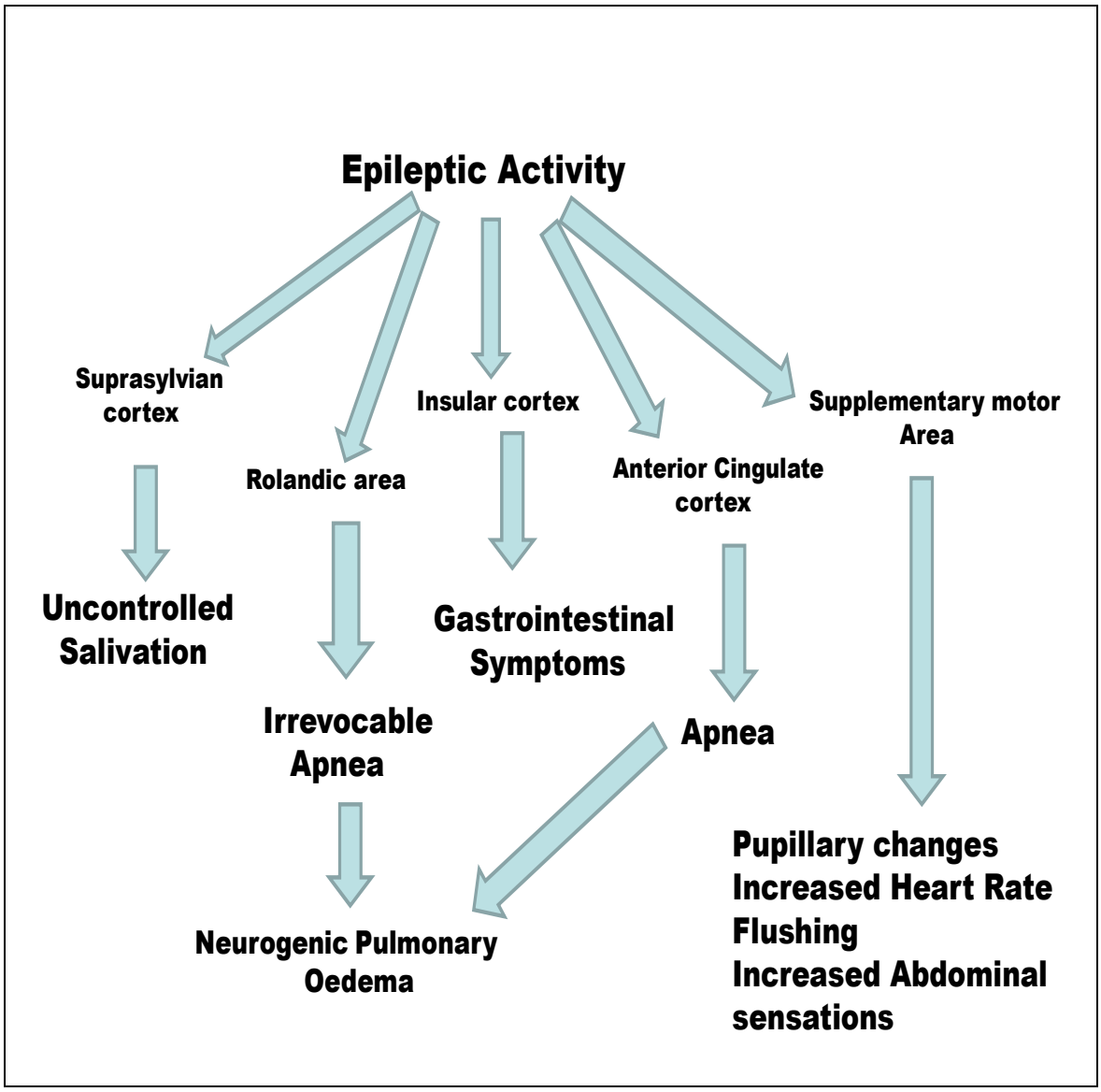


Figure 1 Illustration of how cortical activity may cause ictal autonomic changes.

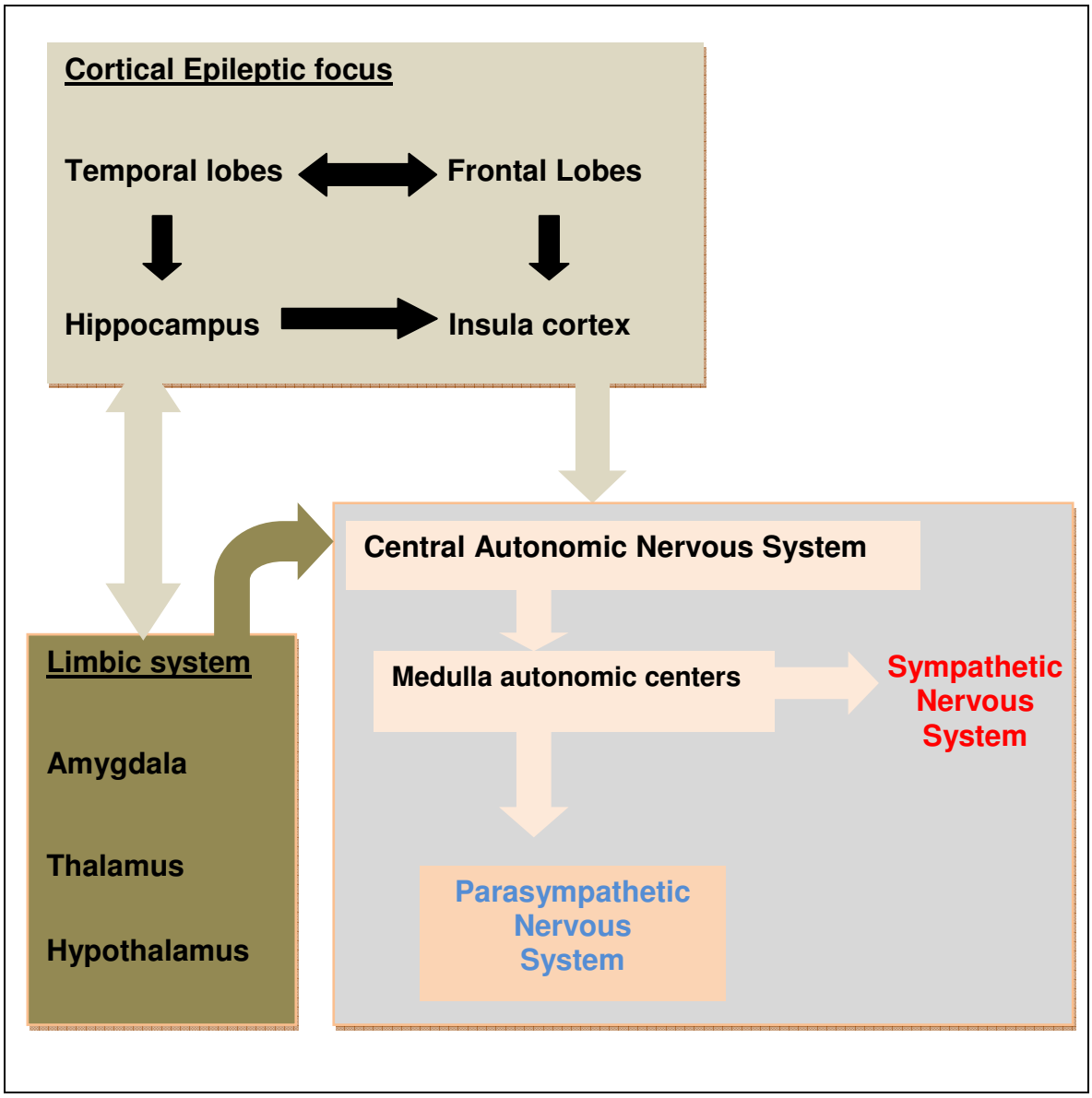


Figure 2 Illustration of autonomic propagation from the cortex to the brainstem cardiorespiratory centres'. There exist reciprocal connections between the limbic system and cortical epileptic foci. The central autonomic network which exerts modulating influence on the peripheral autonomic system is directly influenced by the limbic system and the epileptic foci. This scheme of hierarchal control is much more complex than presented here.

To understand the relation between epilepsy and the autonomic nervous system, I will discuss three themes:

- The effects of epilepsy on the autonomic nervous system (Section 2.2.1)
- The effects of the autonomic nervous system on epilepsy (Section 2.2.2)
- The clinical consequences of this interaction (Section 2.2.3)

2.2.1 The effects Epilepsy has on the Autonomic Nervous System

Autonomic changes in Generalized Tonic Clonic Seizures

During generalized tonic clonic seizure, massive autonomic changes occur predominantly during the ictal period. Autonomic changes in generalized seizures have been documented through monitoring of general body physiology following experimental electroconvulsive therapy. In electroconvulsive therapy, earlier researchers were able to describe a specific pattern of increase in the heart rate, blood pressure and intravesical pressure at the onset of a generalized tonic-clonic seizure, peaking at the end of the tonic phase and returning progressively to pre seizure levels at the end of the clonic phase (Mosier et al. 1957; Panayiotopoulos 2007). Whilst cardiac autonomic indices increase, respiratory rate falls suddenly, patients experience apnoea and respiratory arrest, which recovers during the clonic phase of a generalized tonic clonic seizure. In some cases, however, these changes continue into and throughout the post ictal phase. These changes are usually not associated with other forms of generalized seizures such as myoclonic, atonic and absence seizures. The acute autonomic response reflects acute vagal activation followed by excessive sympathoadrenal activation; these are independent of the associated excessive muscular activity.

These autonomic responses can be complicated by arrhythmias and neurogenic pulmonary edema, the mechanism of which is said to be a consequence of excessive sympathoexcitation of the pulmonary vascular bed. This causes an increase in pulmonary vascular pressure which in contrast to the associated transient increase in systemic vascular pressure, is independent of the number of seizures and persists for a much longer time. Fatal arrhythmias complicating electroconvulsive induced seizures have been prevented by the use of assisted ventilation with 100% oxygen (Bennaroch 1997). It is not surprising that sympathetic-mediated neurogenic pulmonary edema

occurring during generalized tonic clonic seizures has been suggested to be a cause of SUDEP, although direct evidence is lacking (Langan et al. 2005; Tomson et al. 2008). Nevertheless, there is a strong association of SUDEP with generalized tonic-clonic seizures, which increases the risk of SUDEP by as much as 4.4% per tonic-clonic seizure in a year when compared to other presumed risks (Surges et al. 2010a). Surges et al in this study also confirmed detrimental cardiovascular autonomic effects to occur more frequently during generalized tonic-clonic seizures. Generalized epilepsy is commonly accompanied by urinary incontinence which is sensitive but not specific to generalized tonic seizures. Urine loss is seen in the clonic phase of generalized tonic clonic seizures when there is generalized relaxation of the vesical sphincter particularly the external component and therefore does not occur in the period of increased intravesical pressure. This only occurs when there is urine in the bladder, coincident with the occurrence of the seizure. In generalized epilepsies, absence seizures may be associated with ictal passage of urine. In children with absence epilepsy the passage of urine may occur due to high intravesical pressures (Baumgartner et al. 2001; Sinclair et al. 2007).

Generalized tonic clonic status epilepticus is associated with prolonged bilateral synchronous brain electrical activity that excites the central autonomic network resulting in a massive sympathetic activation and a host of autonomic symptoms including hypertension, tachycardia, hyperglycaemia, neurogenic pulmonary edema, and an abnormal thermoregulatory response. These are mediated through a neurogenic release of catecholamines, insulin and glucagon. Arterial hypertension is associated with increased intracranial pressure and a simultaneous parasympathetic discharge all of which can induce fatal cardiac arrhythmias. Hypotension eventually develops during the refractory stage of status epilepticus because of the massive metabolic overload, down regulation and desensitization of the catecholamine receptors. Cerebral auto-regulation which is under autonomic reflex control also becomes dysfunctional creating pressure dependent cerebral blood flow, which as hypotension persists, may result in cerebral ischemia (Bennaroch 1997). In addition to the above, several other symptoms attributable to the autonomic system occur in generalised tonic clonic seizures; these are tabulated below (Table 1) and are illustrated in the classic monograph of Gastaut and Broughton (Figure 3).

Table 1 Autonomic signs in different body systems during GTCS

System	Effects
Cardiorespiratory	Increase in heart rate and blood pressure, Hypoventilation with apnoea and hypoxia
Genitourinary	Increase in intravesical pressure culminating in urinary incontinence in the clonic phase.
Pupils	Pupils dilate become unresponsive to light and some patients may develop hippus. Miosis is extremely rare.
Skin	Skin colour changes cyanosis with apnoea pallor in the immediate post ictal phase and piloerection and sweating.
Glandular secretion	Hypersalivation, Tracheobronchial hypersecretion and marked sweating.

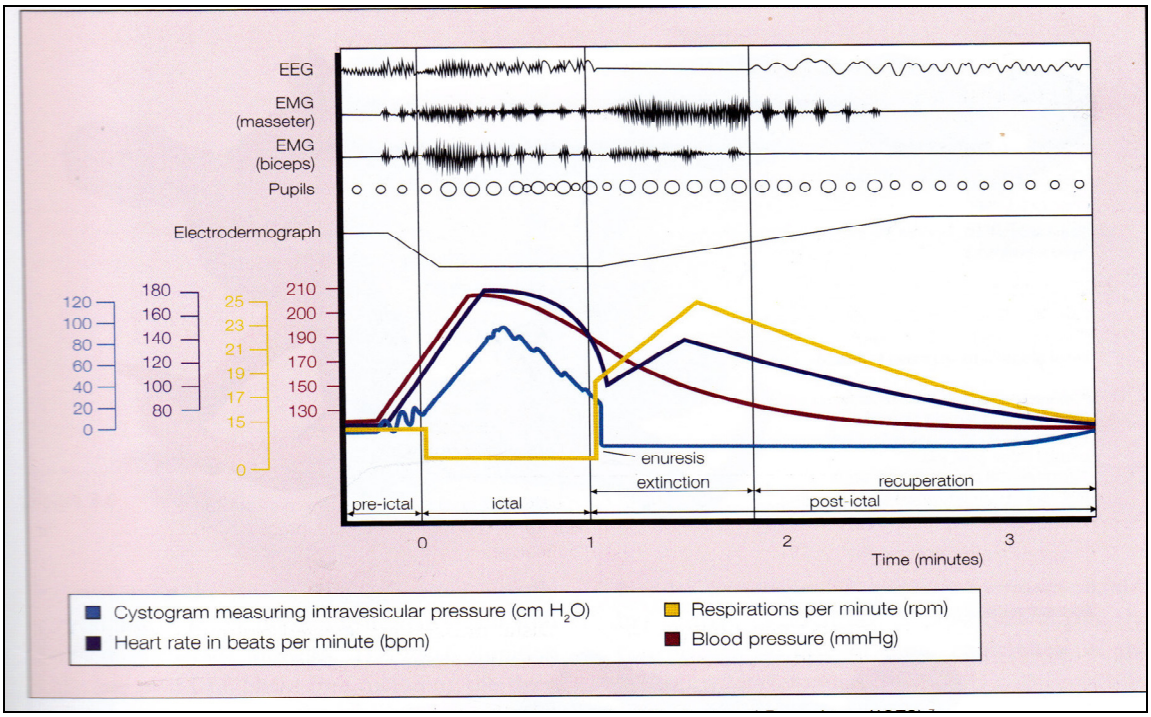


Figure 3 Figure taken from the Classic monograph of Gastaut and Broughton showing the autonomic changes seen in generalised tonic clonic seizures. Source: A clinical Guide to Epileptic Syndromes and Their Treatment 2nd Edition. C. Panayiotopoulos, 2007.

Autonomic Changes during Partial Seizures

This form of epilepsy is associated with a variety of auras and signs that clearly indicate the involvement of the autonomic nervous system by epileptic activity. Paroxysmal activity arising from the amygdalo-hippocampal, orbitofrontal, opercula, cingulate and anterior frontopolar regions can produce various autonomic manifestations. The majority of these areas are a part of the limbic system and by virtue of their extensive connections with the central autonomic centres including the hypothalamus, medulla and spinal cord, can affect the peripheral sympathetic and parasympathetic autonomic outflows (see figure 5 and 6). Several old stimulation and observational studies helped to delineate the localisation of cortical discharges and autonomic function. Jasper and Penfield observed that autonomic signs during partial epilepsy vary and depend on the brain region involved but were not correlated with the pattern of the electroencephalogram (EEG) e.g. slow or fast rhythmic spike wave discharges (Penfield et al. 1957). After Penfield's characterisation of autonomic function and brain areas, Van Buren, demonstrated, in a series of experiments, using both spontaneous and induced attacks that bradycardia, reduction in skin resistance, increased oesophageal activity and apnoea can occur at the onset of partial epilepsy (Van Buren et al. 1961).

Following this, Van Buren, again used stimulation experiments to show a strong correlation of the involvement of the amygdala and neocortical temporal lobe with the autonomic nervous system (Van Buren 1961). Later experiments measured the latency to the development of autonomic cardiac symptoms after stimulation of specific cortical areas and found that, on stimulation of the amygdala, some had short latencies, whilst others had much longer latencies to the onset of cardiac symptoms. When prolonged the implication is that other cortical areas were being recruited (Lathers et al. 1982; Lathers et al. 1987). Stimulation and ablation experiments have also demonstrated that autonomic function is related to activity in the septal area, preoptic area and the hypothalamus which are modulated by the limbic system structures in the temporal lobes (Lathers et al. 1982). The temporal lobe structures, amygdala and hippocampus have a role in modulating hypothalamo-pituitary secretions. Epileptic activity related to these areas may therefore cause clinically recognizable peripheral autonomic symptoms. The amygdala stimulates and the hippocampus inhibits pituitary ACTH release. When

both act together they increase the release of growth hormone and thyroid hormone releasing hormone from the pituitary. In stimulation experiments it has been found that the amygdala alone increases hypothalamic gonadotropins and prolactin secretion in humans (Lathers et al. 1982). It is therefore not surprising for a number of sexual function disorders to be present in chronic epilepsy patients (De Vincentiis et al. 2008; Demerdash et al. 1991; Hilz 2008; Kuba et al. 2006; Luef 2008; Zelena et al. 2007). Autonomic function in partial seizures can be more easily characterised than autonomic function in generalised tonic clonic seizures. The systems most commonly affected are the cardiovascular system and the gastrointestinal system. Alterations that occur in the respiratory system, the genitourinary, the pupils and the skin and integument are not uncommon. It is likely that a partial seizure will cause significant disruption to autonomic function only when the ictal discharge propagates to areas of the brain that subserves the central autonomic network, and this is one of the topics explored in this thesis. Autonomic symptoms occurring in partial seizures are usually isolated and restricted to particular organ systems and in some cases are useful in the diagnostic assessment such as the epigastric rising sensation commonly described by patients with mesial temporal lobe epilepsy (Goodman et al. 2008). The occurrence of autonomic phenomena, especially cardiac related autonomic dysfunction during epilepsy, may result in difficulties in diagnosis, particularly in differentiating syncope from epilepsy. The rest of this section is devoted to autonomic signs in partial epilepsy categorised by the end organ.

Autonomic signs of the eye in partial epilepsy

Autonomic symptoms in epilepsy involving the eye commonly affect the pupils which contains effectors subserved by the autonomic nervous system. Bilateral pupillary dilatation has been described in both partial and generalised seizures. Unilateral pupillary dilatation also occurs but has no significance in lateralising the seizure in focal epilepsy syndromes. Sustained pupillary dilatation and hippus (rhythmic contracting and dilating pupils) frequently occur in generalised epilepsy (Panayiotopoulos 2007). The other autonomic effector in the eye is the lacrimal gland involved in tear generation. Ictal crying has been occasionally reported in the symptomatology of temporal lobe epilepsy (Fogarasi et al. 2007; Hogan et al. 2006; Kutlu et al. 2005); crying is a common symptom of psychogenic non epileptic attacks(Bergen et al. 1993). Apart from being an

ictal manifestation, crying has been recently described to be a precipitant for seizures(Yamamoto et al. 2007). This may be an instance where stimulation of the autonomic nervous system results in epileptic seizures. However crying is a parasympathetic response and it is more usual for the sympathetic arm of the nervous system to modify the occurrence of seizures (Nagai et al. 2004).

Autonomic manifestations of the cardiovascular system in partial epilepsy

Seizure induced autonomic dysfunction of the cardiovascular system is thought to be possibly one of the major factors underpinning the excessive mortality of patients with epilepsy compared to the general population. Mortality in epilepsy includes seizure related deaths, accidents and physical injury and the sudden unexpected death syndromes (SUDEP). There is evidence from experimental animal models that intense sympathetic stimulation of the heart can result in subtle cardiac lesions; such lesions have been found in SUDEP patients and have been hypothesized to act as a nidus for fatal arrhythmias after sympathetic stimulation. In addition to these chronic effects autonomic dysfunction during seizures can have an acute effect on the heart. Several abnormal rhythms occur in epilepsy and include; Atrial premature beats, paroxysmal supraventricular tachycardia, enhanced sinus arrhythmia, acceleration and deceleration of heart rate, atrioventricular conduction blocks of various degrees, asystole and ventricular ectopies (Blumhardt et al. 1986; Howell et al. 1989; Opherk et al. 2002a; Tigaran et al. 2002; Zijlmans et al. 2002). Tachyarrhythmia's and hypertension are the most common cardiac related autonomic symptoms in partial and generalized seizures (Keilson et al. 1989). Sinus tachycardia occurs most frequently in 60-100% of epilepsy patients during seizures, preceding, following or coinciding with the electrographic discharge (Di et al. 2004; Leutmezer et al. 2003). The clinical significance of this for SUDEP remains unclear; some authors have suggested that it is a possible diagnostic tool to be used in non epileptic seizures (Opherk et al. 2002b). Tachycardia as a symptom of seizures is particularly associated with temporal lobe seizures (Keilson et al. 1989). Certain features such as dystonic posturing, automatisms, automatic behaviour and prolonged duration of seizures are associated with higher incidence of cardiac tachyarrhythmia (Garcia et al. 2001; Nei et al. 2000). In a study that assessed 107 seizures, recording the EEG and the ECG simultaneously, more than 83 % showed tachycardia, defined as the heart rate increasing greater than 10 beats per minute from

the base line during the ictal phase (Schernthaner et al. 1999). Several authors have tried to link ictal tachyarrhythmia with specific anatomical sites (Leutmezer et al. 2003; Weil et al. 2005) and the left mesial temporal lobe focus has been the frequently cited anatomical region for the induction of tachyarrhythmia in seizures. However, these studies used extra cranial scalp electrodes and when intracranial depth electrodes were used, there was no significant laterality in tachycardia from the temporal lobe seizures, and furthermore the involvement of the amygdala could not explain the source of increased heart rate. It is rather the pattern of ictal spread that is important in generating the ictal tachycardia (Epstein et al. 1992). Ictal sinus tachycardia also occurs in gelastic seizures due to hypothalamic harmatomas, which also causes hypertension and peripheral vasoconstriction in addition to the tachycardia (Cerullo et al. 1998).

In childhood epilepsy, available studies on ictal tachycardia are limited, but it has been observed that there is a higher percentage of tachycardia in childhood complex partial seizures of temporal lobe origin when compared to those in adults (Mayer et al. 2004). Angina like pain which may be as a result of indirect autonomic influences has been described in the literature as a cardiac manifestation of localization related seizures. Devinsky described five such patients of which more than half were admitted to coronary care units based on the clinical presentation of sudden onset radiating chest pain associated with sweating , dyspnoea and nausea, very typical of acute myocardial ischemia but these were accompanied by tell tale signs of complex partial seizure, generalized flushing, eye blinking and pupillary dilatation. There was no evidence of myocardial ischemia such as elevated cardiac enzymes, and these patients responded to antiepileptic drugs instead of anti-angina drugs (Devinsky et al. 1986). Interestingly in one case the symptoms were similar to the symptoms of phaechromocytoma which further supports the presumed dysfunction of the autonomic nervous system in epilepsy. Experiments in animal models of epilepsy demonstrate alterations in autonomic inputs to the heart; the cardiac autonomic alterations that were observed in this experiment always occurred before any changes could be seen on the scalp electroencephalograph (Lathers et al. 1987). Abnormal cardiac autonomic activity is observed in the interictal state as well and in some studies, the heart rate variability was consistently reduced in patients with temporal lobe epilepsy in the interictal state irrespective of the antiepileptic drug used (Ansakorpi et al. 2000; Ansakorpi et al.

2002b). The heart rate variability can be calculated using R-R intervals analysis from simultaneously recorded ECGs, during seizures to determine the predominant autonomic input to the heart. In one such analysis it was found that parasympathetic activity declined rapidly in the 30 seconds before the seizure whilst the sympathetic activity increased exponentially peaking just before the seizure (Toichi et al. 1998). Ictal Bradycardia is less common during seizures (Howell et al. 1989). However, occasionally the bradyarrythmias may be severe enough to cause sinus arrest and asystole. Cardiac asystole is infrequent but there are several recent case reports of this phenomenon (Carinci et al. 2007; Howell et al. 1989; Mascia et al. 2005; Novy et al. 2009; Rugg-Gunn et al. 2000; Schuele et al. 2008; So et al. 2007; Strzelczyk et al. 2008; Surges et al. 2009b). There are also several cases where patients with frequent epileptic induced bradyarrythmias have had a cardiac pacemaker inserted (Kiok et al. 1986). Ictal asystole and bradycardia has been found to be associated with temporal lobe epilepsy (Constantin et al. 1990). The left hemisphere is presumed to be the most common site of origin of ictal related bradycardia (Tinuper et al. 2001).

There is therefore no doubt that altered cardiac function may occur in epilepsy. The disturbances in function are presumed to be due to disturbances of the central autonomic network, the peripheral autonomic nervous system and the heart itself. The mechanism of these imbalances of sympathetic and parasympathetic function is still not clearly understood, and it is not clear whether it is a pure epileptogenic related phenomenon or other factors such as drug use and withdrawal or the heightened peripheral muscular activity also contribute.

Autonomic manifestations of the respiratory system in partial epilepsy

Seizures affect the control of respiration as well. Signs of respiratory autonomic dysfunction during partial epilepsy are common. Descriptions of ictal autonomic respiratory phenomena have been made since the middle of the 19th century. Reynolds was the first to mention in 1861, that the breathing of some epileptic patients during seizures became irregular. Later in 1885, Gower's published descriptions of dyspnoea and respiratory spasm which he called choking fits of adults. Subsequently several descriptions of respiratory related autonomic phenomena during seizures have been mentioned in the literature including apnoea, stridor, coughing, postictal nose wiping

and hyperventilation (Baumgartner et al. 2001). Automaticity of respiration is controlled by the central respiratory oscillators located in the lower brain stem. These brainstem oscillators are under the influence of forebrain cortical areas: hippocampal formation; anterior cingulate gyrus; insula; basal forebrain and the motor strip area. These structures are extensively involved in localization related epilepsy and partial seizures arising from the cortex in these forebrain areas could affect respiration. In early stimulation experiments, activation of these areas resulted in irregular breathing patterns, end expiratory apnoea, and hyperpnoea (Van Buren 1958). Temporal lobe epilepsy by virtue of the anatomic location of the epileptogenic lesion is commonly associated with apnoea and oxygen desaturations (Ives et al. 1996) and in one of the patients consented for this study, oxygen desaturations were recorded with ictal events.

The mechanism and clinical correlate of the desaturations are not entirely clear but it may be related to the inhibition of ventilation by the forebrain structures described above (which include the temporal lobe) and in some cases could result in severe compromise of the cardiorespiratory system (Baumgartner et al. 2001). Apnoea during partial epilepsy may be the pulmonary equivalent of the ictal bradycardia syndrome. Apnea as a manifestation of epilepsy is almost always accompanied by muscle jerks, eye twitches, and other tonic body movements without bradycardia in contrast to the apnoea that is associated with bradycardia. It is however not difficult to appreciate because the cardiopulmonary reflexes will initiate a tachycardia when apnoea occurs (Kara et al. 2003). Nevertheless, bradycardia has still been described together with apnoea during partial seizures (Coulter 1984; Fenichel et al. 1980). Hyperventilation does not readily occur in the autonomic semiology of seizures however it is prominent in complex partial seizures in which fear or panic occurs as part of the symptom complex. Since it occurs frequently in psychogenic nonepileptic attacks, careful evaluation using video and ambulatory EEG, might help in identifying hyperventilation with true partial epilepsy (Baumgartner et al. 2001).

Autonomic manifestations of the gastrointestinal system in partial epilepsy

Visceral signs have been long described with partial seizures, probably first described by Morgagni in an elderly patient who had paroxysms of right upper quadrant pain, nausea and vomiting (Freeman et al. 2008). Whether this was due to paroxysmal dysfunction of the central autonomic network (CAN) or arising from his epilepsy was however not documented. Panayiotopoulos syndrome is by far the commonest gastrointestinal autonomic manifestation of epilepsy. This occurs in childhood. The symptoms of Panayiotopoulos syndrome are autonomic and include recurrent nausea, vomiting, pallor and flushing. What is striking in this syndrome is the prominent gastrointestinal signs related to cortical electrical activity (associated EEG occipital spikes), occipital in origin, that are postulated to spread to the vomiting centres' of the hypothalamus and the medulla (Panayiotopoulos 2007). In adult epilepsy, the commonest gastrointestinal autonomic signs are the gastrointestinal (GI) auras and these occur more frequently than cardiovascular manifestations.

The gastrointestinal signs include: vomiting, retching, cramping abdominal pain, diarrhoea, urge to defecate, faecal incontinence, bloating, borborygmi, periumbilical pain, butterflies in stomach, feeling of hunger. These symptoms have been obtained by stimulating the amygdala, hippocampus and insula cortex. These visceral symptoms are not due to dysfunctional GI motility but rather to abnormal sensory percept because gastrointestinal smooth muscle is unaffected during these periods (Baumgartner et al. 2001; Van Buren et al. 1960). In addition to the above signs, retching and vomiting associated with loss of consciousness can occur in the ictal period as the sole manifestation seizures (Baumgartner et al. 2001; Catenoix et al. 2008; Mitchell et al. 1983). Conflicting results have been described with regards to the hemispheric laterality of the focus of gastrointestinal signs. Whilst, some studies lateralize to the right (Devinsky et al. 1995; Gupta et al. 1983; Kramer et al. 1988), other investigators have not found this (Gil-Nagel et al. 1997; Marks, Jr. et al. 1998). However gastrointestinal signs generally localize to the temporal lobes regardless of side (Baumgartner et al. 2001).

Autonomic signs of the genitourinary system in partial epilepsy

In partial seizures micturation without loss of awareness is rare. Indeed, it is unusual to have urinary incontinence during partial seizures, and urinary urgency without incontinence is more frequent (Baumgartner et al. 2000; Baumgartner et al. 2001; Panayiotopoulos 2007). The autonomic innervations of the bladder and internal bladder sphincter are by branches of the peripheral autonomic system located in the sacral plexus, functions of which are modulated by the urinary control components of the central autonomic network. Whilst parasympathetic stimulation causes detrusor muscle contraction and passage of urine, sympathetic stimulation of the urinary bladder decreases bladder pressure and filling time so as to limit the number of micturation episodes. The basis for the urge to urinate experienced during partial seizures is not entirely clear. In healthy individuals the urge to urinate is not automatically followed by passage of urine. In addition, fullness of urinary bladder and intense anxiety increases the desire to void (Athwal et al. 2001; Holstege et al. 2008).

One postulation has been that the urinary urgency in partial seizures is due to anxiety but there is no scientific data to support this. What is clear is that the coordination of micturation activity is by interrelation between brain and brainstem structures particularly the anterior cingulate gyrus, periaqueductal gray, the hypothalamus and several other central structures (Holstege et al. 2008). These constitute the central autonomic network and are the same areas involved in the urge to urinate. These symptoms also occur in temporal lobe epilepsy which is not surprising because of the extensive connections that exist between the components of central autonomic network and the temporolimbic pathway. It is not clear why ictal urinary urgency is commoner in right hemisphere epilepsy, but it provides evidence to support the presumed asymmetry of central autonomic influences on target organ (Adjei et al. 2009; Oppenheimer et al. 1990; Oppenheimer et al. 1992; Zamrini et al. 1990).

Autonomic signs of sexual function in partial epilepsy

Human sexual function is affected by autonomic dysfunction. The extent to which sexual organs respond to sexual stimulation depends on the integrity of the central autonomic network and the innervations of the genitals by the peripheral autonomic nervous system. According to the *ICD10* and *DSM IV*, there are four main categories of human

sexual dysfunction; arousal disorder, disorder of "sexual desire", disorder of orgasms and pain. All of these disorders are described in patients with chronic epilepsy (Hilz 2008; Morrell 2008). In epilepsy, the epileptic syndrome, seizure frequency and the antiepileptic drugs used influence sexual function. However, the majority of men and women with epilepsy have normal sexual lives (Crawford 2005). There are two broad categories of sexual dysfunction; phenomenological and dysfunctional sexual behaviours, both of which occur in epilepsy. Phenomenological sexual behaviours are paroxysmal in context and constitute part of the symptom complex in epilepsy described as "sexual auras". They manifest as deep seated erotic thoughts, sexual arousals, sexual orgasms, genital sensations, erections, ejaculations, increased vulvovaginal secretory activity and "genital automatisms" which may not be related to autonomic function but are sexual in context and include: exhibitionism, fondling, grabbing, manipulation of the external genitalia, rhythmic and controlled movement of the legs, pelvic thrusting and even masturbation (Freeman et al. 2008). Whilst Janszky reported the auras to be common in women patients with epilepsy and mostly associated with right temporal lobe epilepsy (Janszky et al. 2004), Dobesberger, in the same year, described genital automatisms to be common in male patients without the right sided laterality but temporal lobe in origin (Dobesberger et al. 2004). The significance of these observations is the involvement of the temporal lobe in the sexual semiology of partial seizures. Abnormal sensations in genital and pelvic areas constituting sexual auras can be mistaken for infantile masturbation, a rather rare condition that may be misdiagnosed as epilepsy, occasionally resulting in antiepileptic drug prescription (Fleisher et al. 1990; Otaigbe 2008; Wulff et al. 1992).

Dysfunctional sexual behaviour, on the other hand is reported interictally (Kutlu et al. 2005; Luef 2008). Human sexual behaviour is controlled by three main factors; libido, arousal and orgasm. Whilst libido is modulated mostly by psychological factors, arousal and orgasms remains a function of the autonomic nervous system. The mechanisms underpinning sexual function abnormalities reported in epilepsy are unknown but probably involve especially the emotional circuitry of the amygdala, increased prolactin levels and the antiepileptic drugs (Bennaroch 1997; Hilz 2008). The progression to orgasm in a seizure is extremely rare but spread to the hypothalamus in temporal lobe epilepsy can be associated with unpleasant or even painful orgasms.

Report is made of the great Russian writer, Dostoevsky, who had a rare form of temporal lobe epilepsy in which he would have sexual fantasies and orgasms during attacks (Morgan 1990). Older female patients with epilepsy have impaired vaginal lubrication and dyspareunia that causes them to have hyposexuality. This leads to a difference in sexual behaviour when compared to adolescents and younger women with epilepsy. The latter group have been found to have similar sexual behaviours as their non epileptic counterparts (Zelena et al. 2007). Autonomic contribution to female sexual function depends entirely on the integrity of the central autonomic structures (amygdala and hypothalamus) and the peripheral autonomic innervations of the female genital organs.

Stimulation of the central autonomic network will cause activation of the two arms of the peripheral autonomic nervous system. The effects of the parasympathetic and sympathetic nervous system on the female sexual response are controversial but evidence available is that sympathetic stimulation causes reduced vaginal blood flow, secretions, vaginal moistening and dyspareunia whilst the converse is true for parasympathetic stimulation (Hilz 2008). In the male patient with epilepsy, hyposexuality, characterized by erectile failure and normal libido has been reported (Kuba et al. 2006; Molleken et al. 2009; Pritchard, III et al. 1983; Siniscalchi et al. 2008). Apart from a presumed autonomic disturbance, the reason for some male patients to experience erectile failure and dysfunction is not fully understood. Many factors, not necessarily autonomic in nature may be at play: including depression, psychosocial deficits such as a low self esteem, endocrinological effects of antiepileptic drugs and restricted social opportunities (Morrell 2008).

Autonomic signs manifest in the skin in partial epilepsy

Seizures generate skin flushing and pallor as well as pilomotor erection, diaphoresis and feelings of warmth and cold, and may modify the generation of sweat which is the basis for the skin resistance. The most described skin manifestations is the “Goose flesh” which is due to pilomotor erection and is always accompanied by other autonomic symptoms in partial epilepsy of dominant. The cutaneous signs, which are temporal lobe in origin, are commonly bilateral. However, on many occasions they can lateralize to a side contra lateral to seizure focus (Drake 1984).

2.2.2 The effects Autonomic Nervous System has on Epilepsy.

A number of clinical observations indicate the level of autonomic nervous system activity may be significant in providing an appropriate environment for the precipitation and occurrence of seizures (Nagai et al. 2004). The evidence alluding to the potential influence of the autonomic nervous system on cortical epileptogenic foci is quite small; however heightened levels of excitement in the autonomic nervous system particularly under extreme forms of stress seem to contribute to seizure susceptibility at least in mesial temporal lobe epilepsy (Koe et al. 2009). Abnormal cardiac rhythms can cause reduced cerebral perfusion and lead to convulsive activity but rarely causes cortical epilepsy. The rare condition, primary eating epilepsy is an example of how gastrointestinal activity (increased motility during eating which is a purely autonomic mechanism) might precipitate a seizure (Rosenzweig et al. 2008). Mechanisms are not fully clear as the bulk of gastric peristalsis associated with eating is parasympathetic and increased sympathetic arousal is rather involved in seizure precipitation. Yoko Nagai, working at the National Hospital for Neurology and Neurosurgery in London, demonstrated an inverse relation between peripheral sympathetic arousal and cortical arousal activity such that in extremely relaxed states when the skin resistance was high enough there was an associated reduction in cortical stimulation. By using behavioural modifications, the authors were able to suggest a management for treatment resistant epilepsy based on relaxation techniques (Nagai et al. 2004).

Stimulation of vagal afferents has been associated with inhibition of several types of experimental seizures (Rutecki 1990). The inhibition is bi-hemispheric, seizures are suppressed within seconds, which lasts for a long time and remains bi hemispheric whether the stimulation is bilateral or unilateral. The neurobiological basis for vagal nerve stimulation and autonomic modulation in the treatment of refractory epilepsy is said to be related to the extensive connections of the main relay station of the vagus nerve, the nucleus of the tractus solitarus, to the hippocampus and other cortical areas involved in the propagation of seizures (Castle et al. 2005), however the exact mechanism is not yet characterised. It has been suggested that it is the release of noradrenalin from the locus coeruleus following stimulation of the vagal nerve that results in seizure suppression (Schachter 2009). As vagal nerve stimulation is now widely

used, further insights may be uncovered for the significant role the autonomic nervous system plays in epilepsy.

2.2.3 Clinical effects of Autonomic abnormalities in epilepsy

Autonomic abnormalities and SUDEP

An early statistical report of unexplained death in patients with epilepsy was by WP Spratling, the eminent American epileptologist and future President of the ILAE, in 1902 who described that up to 4 percent of deaths in a population of epileptic patients occurred without any identifiable explanation. Subsequently several retrospective and prospective studies on unexplained death in epilepsy has been conducted and overall, sudden death has been found to be increased in patients with epilepsy by as much as 24-40 times the general population (Freeman 2006; Langan et al. 1998; Langan 2000; Langan et al. 2005; Opeskin et al. 2003; Timmings 1998; Walczak et al. 2001). Mortality among epilepsy patients is of 2-3 times higher than the general population. SUDEP account for as much as 10- 15 % of mortality in epileptics and this exceeds that due to status epilepticus. In people with epilepsy, the annual incidence of SUDEP is of the order of 1 in every 500 to 1000 patients depending on the population under investigation (Leestma et al. 1989).

The term SUDEP has been defined by Nashef (1997) and this definition is now universally accepted. According to this definition, SUDEP is: The sudden, unexpected, witnessed or unwitnessed, non traumatic, and nondrowning, death in patients with epilepsy with or without evidence of seizure and excluding documented status epilepticus , in which post-mortem does not reveal a structural or toxicology cause for the death (Nashef 1997). The cause for SUDEP may be multifactorial but it is presumed in most instances to be due to unexplained respiratory failure, cardiac arrhythmia during or in the immediate aftermath of a seizure in most cases. The mechanism of the cardiac and respiratory disturbances have an autonomic response (Blum et al. 2000; Kiok et al. 1986; Lathers et al. 1982; Lathers et al. 1987; Nashef et al. 1996; Rugg-Gunn et al. 2000). The occurrence of generalized tonic clonic seizures is the most important risk factor for SUDEP but this is not to say that SUDEP only occurs in patients with chronic uncontrolled epilepsy who may have the supposed risks but occurs even in patients with rare seizures as well (Opeskin et al. 2003). The pathological findings in SUDEP have been reviewed by Thom

(2003) (Thom et al. 2003). Most striking is pulmonary edema which is a common finding at autopsy in patients who have had SUDEP (Colice et al. 1984; Malik et al. 1994) but is not usually severe. Such oedema is thought to be neurogenic due to excessive ictal sympathetic discharge to the pulmonary vasculature during generalized tonic clonic seizures. Interictal and ictal arrhythmias occur in epilepsy, as well as a marked ictal catecholamine surge during a fit and if high enough can itself cause cardiac arrhythmias and sympathetic myocardial injury in patients with epilepsy (Legriel et al. 2008). Sakamoto (2008), in an animal model experiment, found simultaneous over-activity in the peripheral divisions of the autonomic nervous system during experimental generalized tonic clonic seizures. He attributed death to a form of asphyxiation where respiratory distress occurring in an epileptic seizure led to profound parasympathetic discharge. This and the ensuing bradycardia compounded with the mechanical failure of the heart due to simultaneous over activity in the parasympathetic and sympathetic nervous system led to sudden cardiac death (Sakamoto et al. 2008).

Autonomic abnormality during seizures and syncope

Loss of consciousness is a frequent clinical presentation. It forms a spectrum, which at one end has patients with acute loss of consciousness due to cardiac arrhythmias during a seizure and at the other extreme, loss of consciousness due to an acute cardiovascular failure. Loss of consciousness in most patients and even in some cases of epilepsy may warrant autonomic function evaluation. The differential diagnosis of loss of consciousness includes syncope and epileptic seizures. Syncope refers to the abrupt loss of postural tone and consciousness' followed by an extremely rapid recovery, due to a sudden and reversible cerebral hypoperfusion (Cook 2009). Syncope has an entirely different pathophysiology and should not be confused with seizures but difficulties arise if there is an increased predisposition to syncope and when syncope occurs in unusual circumstances. Syncope is common but the real cause for more than a quarter of cases of syncope cannot be identified (Mathias et al. 2001). The importance of syncope in epilepsy lies in the extent to which ictal autonomic phenomena particularly "ictal arrhythmia syndrome" can cause syncopal like events during seizures. Syncope may be evident in central nervous system disease and syncope due to sinus arrest during temporal lobe seizures may occur. In fact, Ghearing and Schuele both have suggested that sudden loss of tone during seizure semiology in patients with temporal lobe

epilepsy to represent ictal asystole (Ghearing et al. 2007; Schuele et al. 2007). There is no doubt that patients with epilepsy have abnormalities in autonomic function (Chroni et al. 2009; Devinsky et al. 1994; Devinsky 2004; Dutsch et al. 2006; Hilz et al. 2002; Persson et al. 2007a; Tomson et al. 1998; Tomson et al. 2008) and because of this some patients with epilepsy may have symptoms similar to syncope. Loss of consciousness during a cardiac event may be associated with myoclonic jerks, tonic spasm and incontinence of urine similar to an epileptic event. These symptoms are due to the release of inhibitory motor phenomenon in the upper brainstem by the transient cerebral hypoperfusion. If these patients are evaluated electrophysiologically, the EEG is usually always normal except when done simultaneously with head up tilt test, which will show gradual slowing of cerebral activity and eventual attenuation typical of cardiac syncope (Brenner 1997). Autonomic evaluation in such patients also reveals reduced heart rate variability.

The most common concomitant of syncope in patients with epilepsy may be the “ictal bradycardia syndrome”. This syndrome is undoubtedly an abnormal autonomic cardiac reflex response due to epileptic seizure when it occurs in the absence of any cardiac conduction defects. Several mechanisms has been proposed for ictal bradycardia but the underlying principle involves activation of the cardiac autonomic reflexes that activates the medullary reflex centres to cause increased vagal discharge and hence bradycardia (Schuele et al. 2008). Some other authors have described the cause to be an excessive vagal discharge from an autonomic reflex triggered by a sudden increase in arterial blood pressure associated with increased catecholamine release during a seizure (Bennaroch 2007), whilst others yet still have attributed it to an uncontrolled peripheral autonomic discharge (Sakamoto et al. 2008). Whatever the mechanism is, it is clear that seizure induced influences on the autonomic nervous system could be the mechanism of ictal asystole in patients with epilepsy. As mentioned above, it has been suggested that bradycardia and subsequent asystole may be a crucial part of the ictal phenomenology of suddenly slumping to the floor due to atonia (Ghearing et al. 2007; Schuele et al. 2007). Reflex syncope is worth mentioning. It is a common presentation at epilepsy clinics that warrants autonomic function evaluation to differentiate from cardiac syncope. The consistent finding in reflex syncope is the existence of prolonged prodromal symptoms rightly confused with the auras of epilepsy, a young age of onset,

usually less than 50 years and the association with orthostatic stress as seen in prolonged sitting or standing. Whilst epileptic syncope may occur unprovoked, cardiac syncope on the other hand will occur during heightened physical exertion even though in some cases it has been reported to occur in the resting supine position. Palpitations at rest will not help to differentiate cardiac syncope from epileptic syncope, because in young patients with epilepsy, palpitations occur as a common symptom (Calkins et al. 1995). Prolonged confusion, usually greater than five minutes and clonic jerks before and during the event may help in establishing epilepsy as the cause of syncope but it is also worthwhile to note that some syncopal episodes may be associated with longer lasting confusion (Panayiotopoulos 2007).

Autonomic abnormalities and interictal alterations of behaviour

There are distinctive interictal behavioural patterns in patients with epilepsy, particularly temporal lobe epilepsy, that are ascribed to be related to the dysfunction of the autonomic nervous system. The central autonomic network controls and coordinates autonomic function with behavioural nociceptive and hormonal response to various environmental stimuli. This is made possible by the reciprocal connections that exist between the cholinergic and monoaminergic centres of the septal area and the brain stem that controls sensorimotor, autonomic and neuroendocrine function depending on the behavioural state of the individual. The significance of these reciprocal connections is that the central autonomic network can influence the processing of emotion and cognitive responses from viscerosensory information. The latter may also influence the central autonomic networks coordination of autonomic and other motor responses (Bennaroch 1997). A review of the limbic system anatomy and physiology supports the key role it plays in processing both internal and external sensory percept to determine through memory, the adequate emotional, autonomic and directed motor responses intended for survival. The temporal lobe is an integral part of the limbic system and it is not surprising that temporal lobe epilepsy is particularly associated with disruptions in behaviour but because of the connections of the limbic system to other cortical areas, extratemporal epilepsy can affect limbic function as well (McLachlan 2009). Alterations in behaviour have been related to the autonomic nervous system. The exact autonomic mechanism remains unknown and the association of autonomic function and interictal

alterations of behaviour at this stage is at best, speculative (Bear et al. 1981; Devinsky et al. 1994).

2.2.4 Antiepileptic drugs and Autonomic Function

Experimental studies indicate an intact noradrenergic system may be required for the anticonvulsant actions of some antiepileptic medications including carbamazepine, phenytoin, phenobarbitone, and valproate and (Quattrone et al. 1978; Schank et al. 2005; Waller et al. 1985). Antiepileptic medications that have a stabilization effect on the neuronal cell membrane have a series of indirect effects on the autonomic nervous system (table 2). Carbamazepine is very much implicated in this sense and a study by a Swedish group (Tomson et al. 1998), identified that carbamazepine tends to decrease the heart rate variability. Carbamazepine has several unwanted effects including QT interval prolongation and in patients with epilepsy, even at therapeutic doses, carbamazepine can produce severe prolongation of atrioventricular conduction and result in severe bradycardia (Ide et al. 2007; Johnson et al. 1997; Kumada et al. 2005; Labrecque et al. 1992; Ladefoged et al. 1982; Parihar et al. 1996; Takayanagi et al. 1998). Carbamazepine has other non autonomic effects and may cause hyposexuality in epileptic patients by reducing serum concentration of di-hydroepiandosterone sulphate (Zelena et al. 2007). The sudden withdrawal of carbamazepine has been found to enhance autonomic sympathetic function in patients with epilepsy (Hennessy et al. 2001). Valproate apart from its effect on the GABAergic system and NMDA receptors is said to increase levels of noradrenalin in hippocampal and brainstem tissue which has been found to suppress epileptiform activity (Weinshenker 2008).

Table 2 Autonomic features of common antiepileptic drugs

Antiepileptic Drug	Autonomic Effects					
	HypT	RD	CA	CAb	AchE	GID
Diazepam	yes	yes	-	-	-	-
Lorazepam	yes	yes	-	-	-	-
Ethosuximide	-	-	-	-	-	Yes
Felbamate	-	-	-	-	-	Yes
Phenobarbitone	Yes	Yes	-	-	-	-
Phenytoin	Yes	-	Yes	-	-	-
Valproate	Yes	-	-	-	-	Yes
Carbamazepine	-	Yes	Yes	Yes	Yes	-

HypT; Hypotension, RD; Respiratory depression, CA; Cardiac Arrhythmia, CAb; Conduction abnormalities, AchE; Anticholinergic effects, GID; Gastrointestinal disturbance.

2.3 Cardiac Enzymes, Troponin T and I in Epilepsy

There are published reports to support myocardial damage during epileptic seizures (Woodruff et al. 2003). Factors responsible could be apnoea and increased myocardial oxygen consumption during seizures. There is however evidence against increased troponin during epileptic seizures (Hajsadeghi et al. 2009; Woodruff et al. 2003). These markers in epilepsy could have relevance to the understanding of the mechanism of SUDEP. Various mechanisms that have been proposed include cardiac related sudden death that may be ischemic, arrhythmic or both (Surges et al. 2009c).

2.4 Electrolytes (Na^+, Ca^{2+}, Mg^{2+} and K^+) in Epilepsy.

The change in the serum concentration of electrolytes affects neuromuscular excitability in the normal healthy individual. Modifications in the serum levels of these ions occur readily during seizures particularly generalized epileptic seizures. The electrolyte balance is easily disturbed in patients with epilepsy as during seizures there is the tendency for alkalosis to develop from an unapparent sympathetically mediated hyperventilation usually at the onset of seizures. The changes in serum electrolytes that are apparent in epileptics are: 1) unaffected serum level of sodium (Na+) in both partial and generalized seizures but with prolonged seizure activity occurring especially in the generalized

epilepsy group, elevated serum sodium is likely to be encountered (White et al. 1992). 2) The retention of salt and water which can be associated with the development of convulsions might be one cause for the catamenial exacerbation of epilepsy in women. This is not an absolute observation because earlier reports on the measurement of the serum sodium of non epileptic controls and epileptics in one study showed no significant difference (Reynolds 1970). Magnesium is essential to the maintenance of neuronal stability in excitable membranes; nerve and muscle and it also maintains an allosteric voltage dependent inhibition of glutamate NMDA receptors. Studies that have measured the serum magnesium have found it to be unaffected during all forms of seizures (Hamed et al. 2004; Hurd et al. 1984; Kurekci et al. 1995; Smith et al. 1982). Nevertheless hypomagnesaemia, hypocalcaemia and hypokalaemia have been previously reported in patients with epilepsy (Ilhan et al. 1999). The total serum calcium in epileptics remain normal in between attacks but during attacks there is a decrease in the serum levels of calcium to the low normal, which occurs just before the onset of the seizure activity (Nzeh et al. 1994). As the seizure progresses' and acidosis develops, a gradual increase in the serum calcium occurs (Natelson et al. 1979a). Another contributory factor to calcium dyshomeostasis in seizures is increased catecholamine secretion. This can contribute to hypocalcaemia by increasing intracellular loading of calcium (Natelson et al. 1979a). Abnormal kinetics of serum potassium (K) also occur in epilepsy. During the interictal period, serum levels of K^+ are normal. However, during and after attacks the serum levels of potassium (K^+) increase and stay elevated for some time especially when the seizure activity is, particularly intense or prolonged as for generalised tonic clonic seizures (White et al. 1992). These dynamic changes of the electrolytes can generate electrical instability of the myocardium and could contribute to SUDEP.

2.5 General overview of the autonomic nervous system

The autonomic nervous system controls visceral functions required for the maintenance of homeostasis of the organism. The heart muscles, respiratory smooth muscle, gastrointestinal smooth muscle, secretory glands of the eyes respiratory tract, the skin, neurohormonal secretion and control are all under autonomic control (Goldstein et al. 2007). Anatomically the autonomic nervous system consists of two main systems; sympathetic nervous system and parasympathetic nervous system. These two divisions together with the central autonomic network and their connections in the brain stem constitute the autonomic nervous system (Barron et al. 1993; Fitzgerald et al. 2007a; Harati 1993).

2.5.1 Sympathetic nervous system

The sympathetic nervous system nerve cell bodies are located in the intermediolateral cell columns of the spinal cord segments from T1 to L3. Axons from these cell bodies course with the ventral rami of the segmental nerves and exit with these nerves via the short myelinated preganglionic fibres to form the paravertebral sympathetic trunk which consists of synaptic ganglia and run alongside the vertebral bodies. Long post ganglionic fibres exit the sympathetic ganglia to innervate the target organs (Figure 5). Target organs have specific adrenergic receptors, alpha and beta receptors. All the preganglionic neurons in the sympathetic system release acetylcholine at nerve endings in their respective ganglia and noradrenalin is released by the postganglionic neurons at their respective target organs (Barron et al. 1993; Fitzgerald et al. 2007a; Harati 1993).

2.5.2 Parasympathetic nervous system

Includes special nuclei of the cranial nerves III, VII, IX and X nuclei and special cell columns located in the sacral spinal cord segments S2 – S4 (Figure 5). The synaptic ganglia are located in or close to the effector organ giving rise to long preganglionic nerves. The receptors involved in neurotransmission are two types: muscarinic and nicotinic with acetylcholine being the main neurotransmitter at both the ganglia and effector organ. Not all body organs are innervated by the two divisions of the peripheral autonomic nervous system and in cases where both are found, the end organ is responsive to only one at anytime due to a high level of autonomic interaction at the ganglia (Figure 4). Peripheral autonomic activation results in various opposing clinical

effects which are tabulated in Table 3 (Barron et al. 1993; Fitzgerald et al. 2007a; Harati 1993).

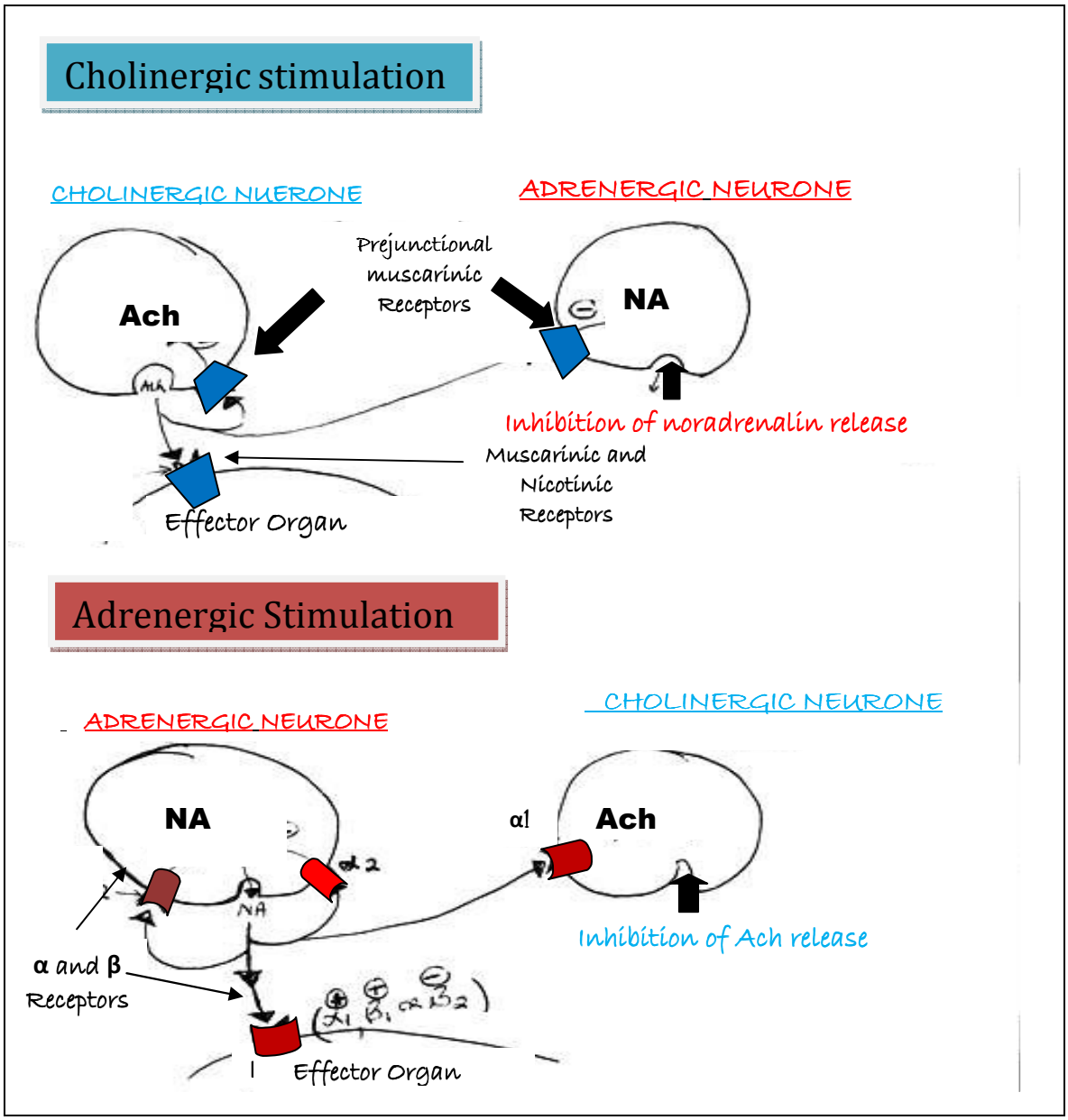


Figure 4 Interaction at the Autonomic nerve effector junction. Adrenergic neurones and cholinergic neurones exist together at nerve effector junctions and there is reciprocal inhibition of a specific neurone following neurotransmitter release through specific pre and post junctional neurotransmitter receptors. This forms the general basis for antagonism in the peripheral autonomic nervous system. Also whilst efferent activity in the parasympathetic system is specific, activity in the sympathetic system is very diffuse affecting several sympathetic effectors simultaneously, in response to afferent stimulation.

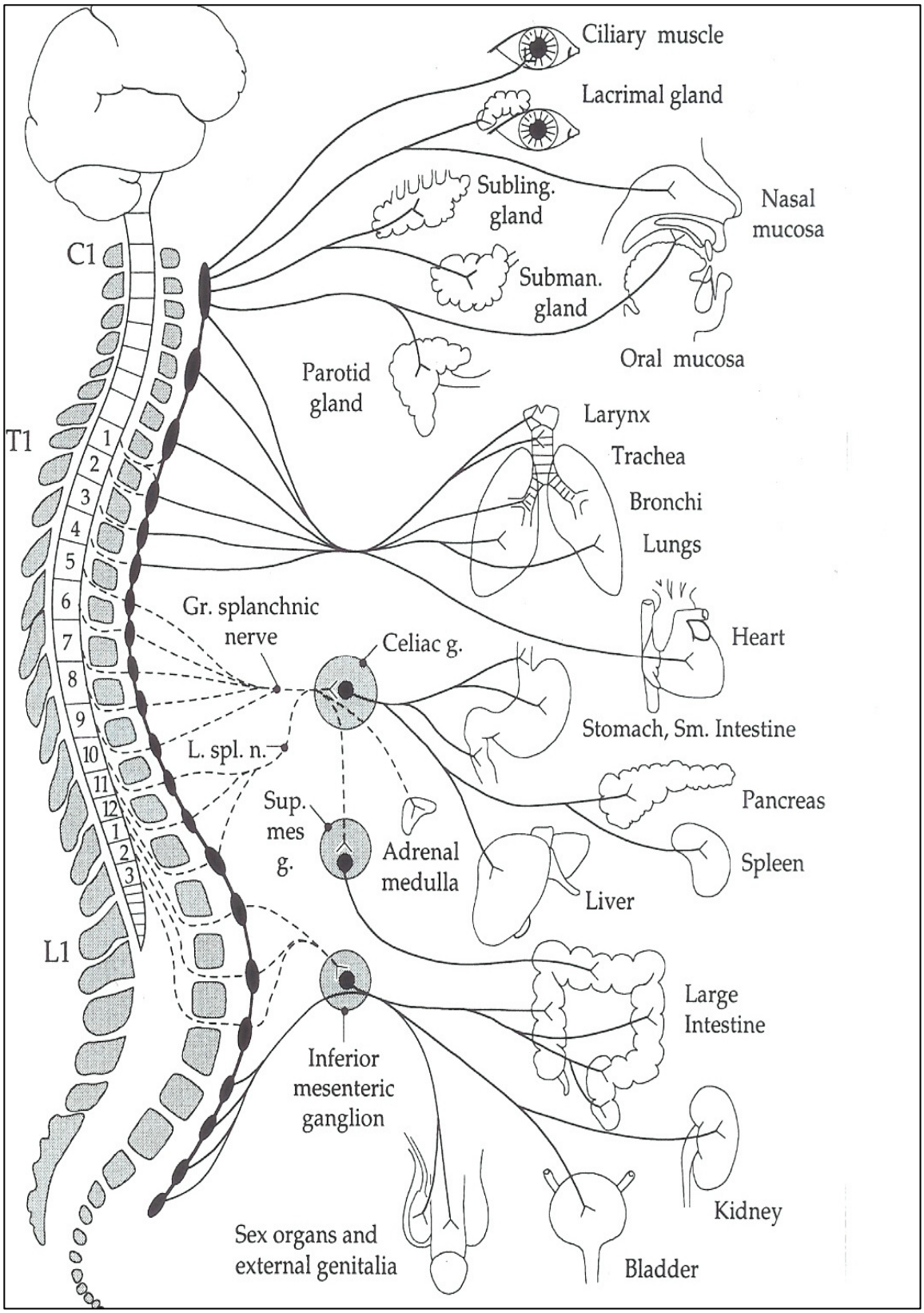


Figure 5 Overview of the sympathetic Innervations in different organs and organ systems. The sympathetic ganglia are located a good distance from the target organ with long postganglionic nerve fibres. Source: Clinical Autonomic Disorders 3rd edition 2007.

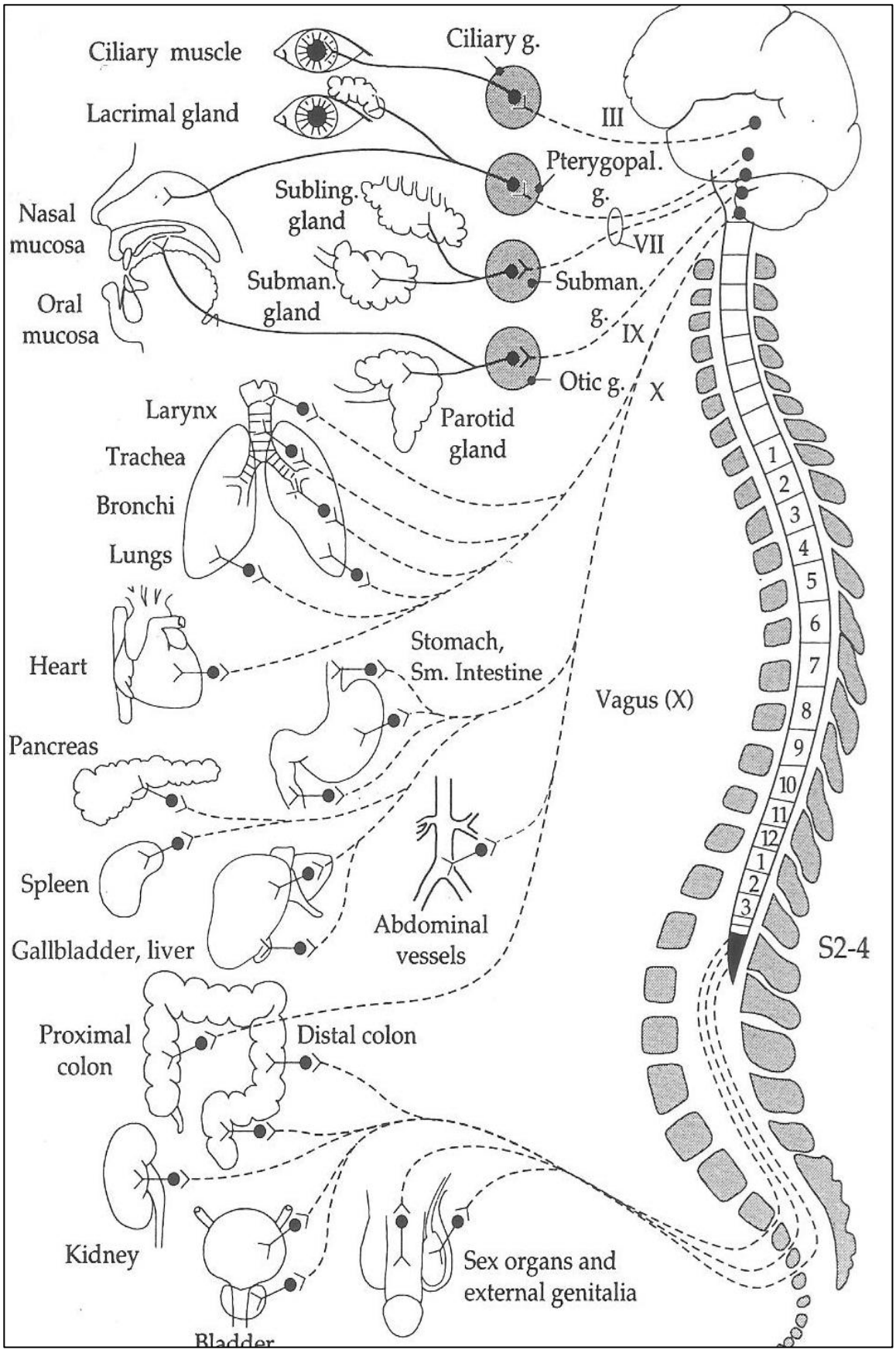


Figure 6 Overview of the parasympathetic innervations of different organs. Autonomic ganglia are located near to or in target organs and the post ganglionic fibres are short. The sacral segments S2-S4 of the spinal cord and Cranial nerves 3, 7,9and 10, form the peripheral parasympathetic system. Source: Clinical Autonomic Disorders 3rd edition 2007.

Table 3 Clinical signs on stimulation of the peripheral autonomic nervous system.

System/Organ	Parasympathetic	Sympathetic
Pineal gland	No effect	Increase melatonin secretion
Brown Adipose Tissue (Infants)	No effect	Heat production
Glands (Exocrine, Salivary, Lacrimal, Nasopharyngeal, Sweat, Digestive and Mucosal)	Increase secretions except for sweat glands where it has no effect	Increases sweat gland activity via a cholinergic sympathetic action but Decreases all other gland secretion
Lymphoid tissue	No effect	Decreases ability of NK cells
Adrenal medulla	No effect	Increases release of NA and AD
Metabolism liver	No Effect	Glycogenolysis and Gluconeogenesis
fat cells	No effect	
Pancreas	Increased secretion	Lipolysis &Decreased secretion
Piloerection muscles	No effect	Contraction
Tracheobronchial muscles	Contraction	Relaxation
Eye	Contracts sphincter pupillae and contracts ciliary muscle only	Contracts all other smooth muscle and the tarsal (lifts eyelid) and orbital (protrusion) muscle
Blood vessels	Effect (vasodilatation)	Vasoconstricts all excepts skeletal where there is cholinergic sympathetic activity causing vasodilatation
Arteries skin face		
skin trunk & limbs		
viscera		vasoconstriction
skeletal muscle		
heart		
erectile tissue		
Veins	Effect (vasodilatation)	
GI sphincters		Contraction
GI Long and Circ muscle	Contraction, all.	
Spleen capsule		contraction

NA: noradrenalin; AD: adrenaline; NK: natural killer. Adapted from Clinical Autonomic Disorders; Evaluation and management. Phillip A Low. First Edition 1993

2.5.3 Central Autonomic Network and the Control of Autonomic Function

This is a complex of neuronal interconnections of specific cortical and brainstem areas which has an adaptive and tonic reflex control on the peripheral autonomic system (Figures 7 and 8). The central autonomic network also controls endocrinological, emotional, and behavioural and pain responses in the intact organism. Central autonomic network activity is state dependent and is affected by the sleep and wake cycle, arterial blood pressure, respiration and a host of other physiologic functions. Neural transmission in the central autonomic network is controlled by the principal central nervous system neurotransmitters Glutamate, GABA, Monoamines, Neuropeptides and Nitric oxide (Bennaroch 2007).

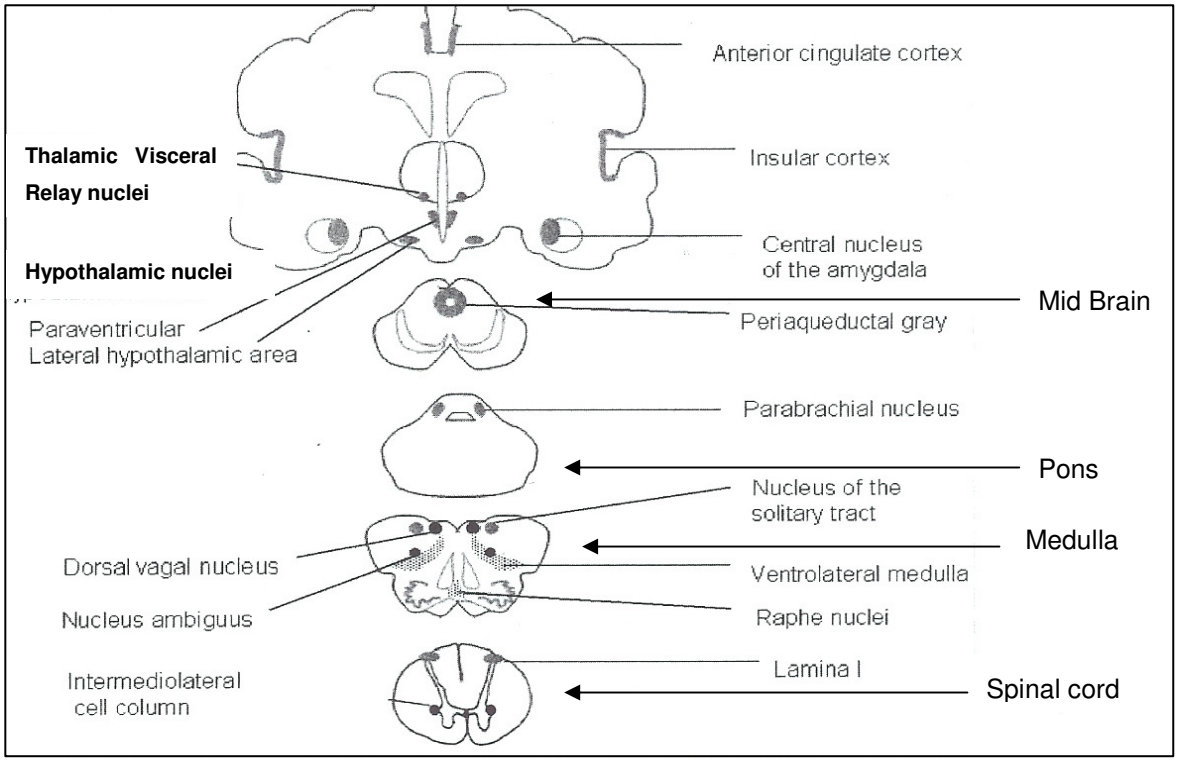


Figure 7 Components of the Central Autonomic Network from the cerebral neocortex to the lower brainstem. The lower segments of the central autonomic network are regulated by the higher centres. Other areas not seen in this diagram are the hippocampus, septal and olfactory areas. Source: Continuum – Autonomic Disorders Volume 13 Number 6 December 2007

The components of the central autonomic network (CAN) are: orbitofrontal, insular, anterior cingulate cortex, amygdala and the hypothalamus constitute the telencephalic components of the central autonomic network**.** These regions control the peripheral autonomic function through both direct and indirect connections with centres in the lower brainstem (NTS, VLM and Medullary Raphe Nuclei). The nucleus of the tractus solitarus (NTS) is the first relay station of autonomic function subserved by the cranial

parasympathetic nuclei to the cerebral cortex and it also responsible for all cardiovascular, respiratory, and gastrointestinal autonomic reflexes. Ventolateral nucleus of the medulla (VLM) provides the major excitatory output for vasomotor tone and the medullary raphe nuclei is responsible for sympathetic outputs involved in thermoregulation and emotional responses (Bennaroch 2007). Stimulation of the insula and other areas of the central autonomic network have helped to delineate the specific functions of the rostral components of the CAN (Reis et al. 1964), interestingly these are the areas commonly involved in the propagation of seizures (Mameli et al. 1988).

Septal Area

This area is adequately described as the ventromedial forebrain. It is a small area merging with the cortex directly in front of the anterior commissure and comprises of the septal nuclei and extends slightly into the septum pellicidum. There are extensive connections from the septal area to other parts of the cortex through the fornix and also to specific areas of the central autonomic network. Activation of this area causes varied autonomic responses including tachycardia.

Anterior Cingulate Cortex

This forms a part of the medial frontal lobe and by means of the papez circuitry connects with the parahippocampal gyrus to form the mesolimbic lobe. It has functional areas that are concerned with autonomic responses (Fitzgerald et al. 2007c). The specific role in the autonomic nervous system is not so clear but bradycardia, hypotension and micturation have been observed from the simulation of this area in rats (Cechetto et al. 1988).

Hippocampal Complex

This is a medial temporal lobe structure consisting of the subiculum, dentate gyrus and hippocampus proper. These structures of the mesial temporal lobe are particularly affected in temporal lobe epilepsy. Clinically, the medial temporal lobe includes the amygdala, hippocampal complex and parahippocampal gyrus. This is connected to the cingulate cortex and the hypothalamus through the interconnections of the papez circuit and epileptic activity in this region can affect autonomic control (Fitzgerald et al. 2007c).

Amygdala

The amygdala is located in the anterior temporal region where it merges with the cortex on the medial side of temporal pole and serves to initiate autonomic responses that are critical for expression of emotions. It's a principal subcortical component of the limbic system with extensive connections to the hypothalamus (Fitzgerald et al. 2007b; Fitzgerald et al. 2007c).

Insular Cortex

This the deep cortical area that includes the temporal, parietal and frontal lobe recesses on the lateral parts of the cerebral hemispheres on either side. Stimulation of this area has been shown to increase the heart rate, blood pressure, the respiratory rate, gastrointestinal activity, epinephrine secretion by the adrenal medulla, piloerection and pupillary dilatation (Penfield et al. 1957). There is an inconsistent body of evidence suggesting that there is lateralisation of autonomic activity in the insula and that right and left insula stimulation results in sympathetic and parasympathetic activity respectively (Oppenheimer et al. 1990; Zamrini et al. 1990).

Olfactory Cortex

This is continuous with the olfactory bulb and it is connected ventrally and laterally to the hippocampus and thus influenced by hippocampal discharges. By means of the medial forebrain bundle the olfactory area connects to the hypothalamus, and the brainstem solitary nucleus and reticular formation (Fitzgerald et al. 2007c). When stimulated there is increased salivation, gastric contraction and erotic arousal responses (Bennaroch 2007; Penfield et al. 1957) .

Hypothalamus

This thermostat organ of the brain is strictly speaking not a cortical structure but one which serves to integrate all cortical inputs to the brainstem components for autonomic regulation particularly the cardiovascular and respiratory centres in the brainstem. It is divided into anatomic functional units; anterior, medial, posterior and lateral areas all sub serving specific functions (Bennaroch 2007; Fitzgerald et al. 2007b). Anterior and posterior hypothalamic activity is associated with parasympathetic and sympathetic function respectively. The fibres for autonomic control in the brainstem section of the

central autonomic neural network remain largely uncrossed as they descend to the lower autonomic centres. The paraventricular nucleus in the hypothalamus has an overall impact on the autonomic nervous system because it has connections to all central autonomic centres. Cardiorespiratory, micturation and vomiting centres in the brainstem are independent of the descending autonomic pathways and can still function even after pontine section (Fitzgerald et al. 2007b). Central autonomic network dysfunction has not been documented in epilepsy patients but cases of paroxysmal disturbance in components of the central autonomic network have been reported in the literature which could be confused for seizures (Uluc et al. 2004). The high volume of interaction (Figures 8, 9a and 9b) that is apparent in the central autonomic nervous system (CAN) is completely absent in the peripheral autonomic nervous system (ANS).

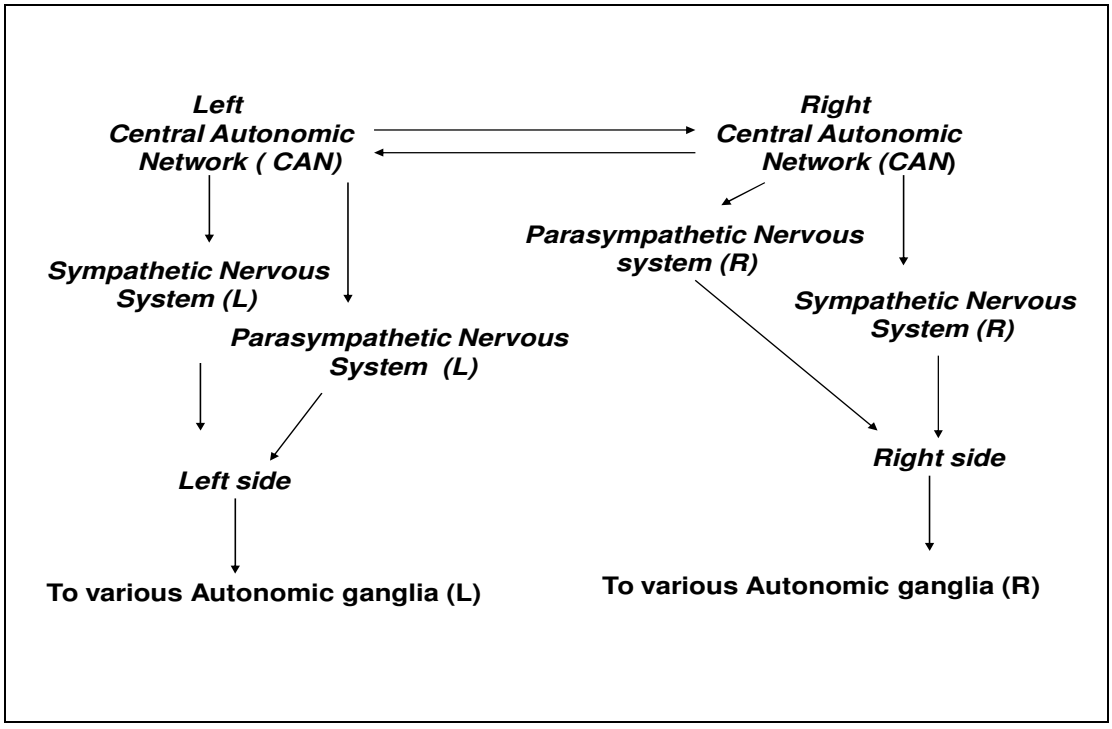


Figure 8 A schematic representations of the complex interconnections of the CAN in the two cerebral hemispheres and also the specific organisation of the peripheral section of the autonomic nervous system into sympathetic and parasympathetic branches which remain lateralised on each side.

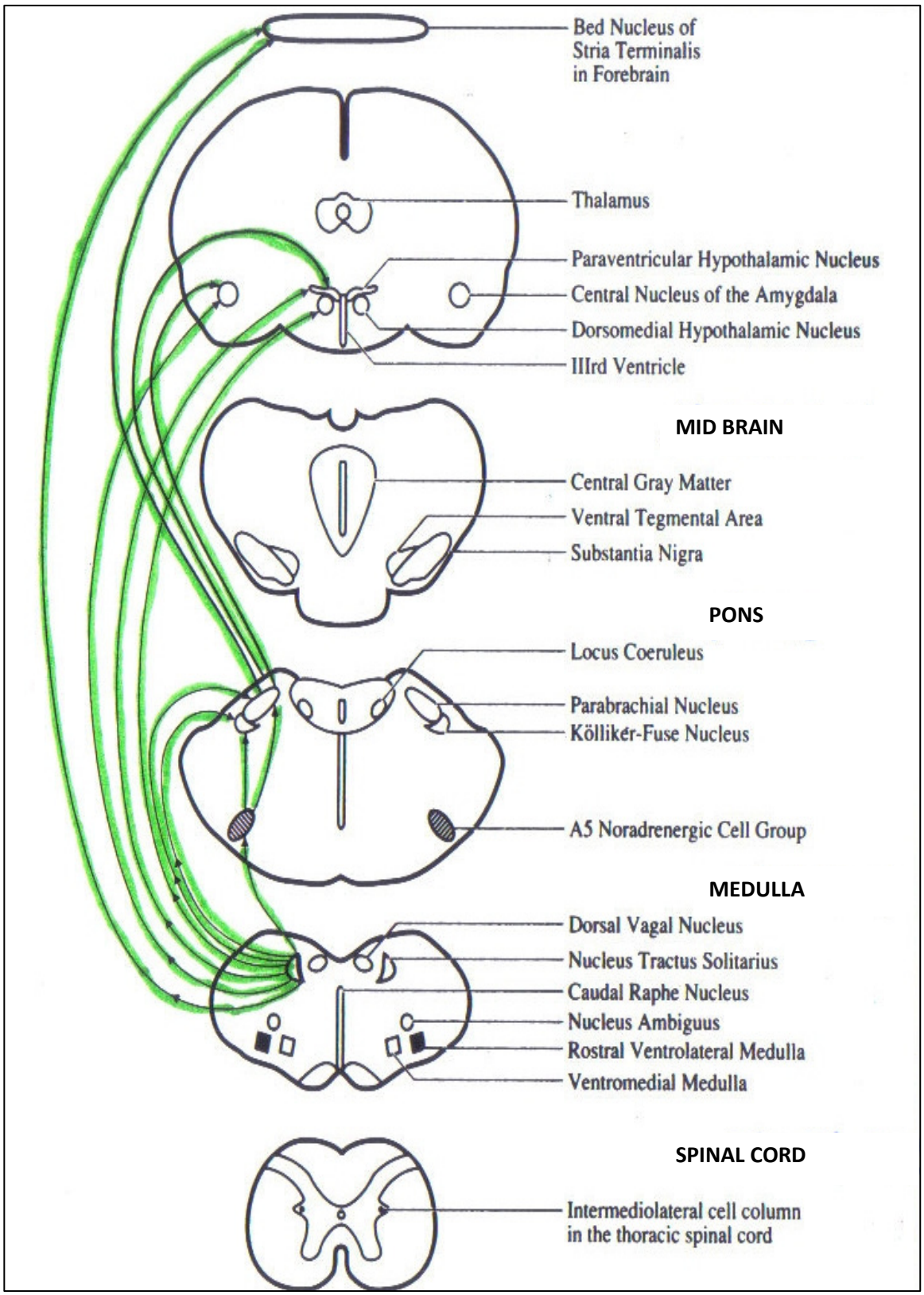


Figure 9a: Ascending Projections of the Central Autonomic Network**.** Together with the descending projection form a reflex arc for integration of inputs of the autonomic reflexes such as the baroreceptor reflexes and the other medullary reflexes. Source: Clinical Autonomic Disorders, 3rd edition 2007.

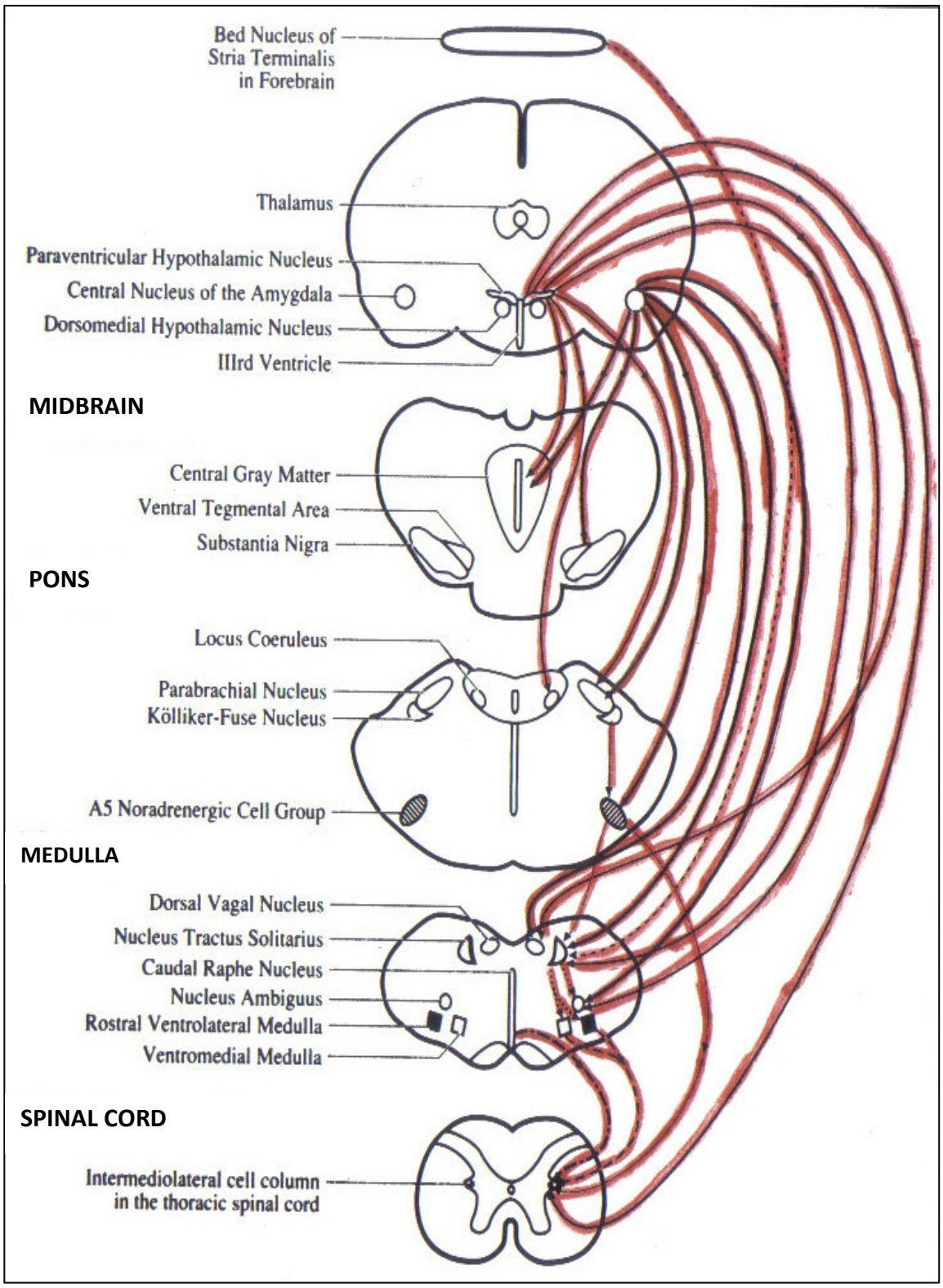


Figure 9b: Descending Projections of the Central Autonomic Network. Injury to the descending pathways innervating the sympathetic ganglia in the spinal cord can result in severe autonomic dysreflexia. The most serious autonomic dysreflexia is an accelerated hypertension that occurs with bladder distension in patients who have developed lesions to the descending pathways above the T5 level in the spinal cord. Source: Clinical Autonomic Disorders, 3rd edition 2007.

The composite structures of the cerebral cortex in the central autonomic network (CAN) have a supervisory role on autonomic control. Many autonomic phenomena arise from stimulation of these structures due to the high level of interconnectivity.

Central nervous system and cardiovascular function

Cardiovascular autonomic control is a function of neuronal activity in the cerebral cortex and other components of the central autonomic network (Talman et al. 1993). Reciprocal connections that exist between the higher and lower centres of the central autonomic network are essential to the integration of this control (Figures 8, 9 and 10).The cardiac pacemaker located to the right of the midline is innervated by the right peripheral autonomic nervous system and the atrioventricular node on the left of the midline has innervations from the ipsilateral peripheral autonomic nervous system (Fitzgerald et al. 2007a). Because of the reciprocal connections in the central autonomic network on both sides of the cerebral hemispheres, asymmetric simulation of one cerebral hemisphere may not be associated with significant changes in cardiac autonomic function. However, direct stimulation of the left and right cardiac nerves have significantly different effects. Where the left cardiac nerve is associated with ventricular and supraventricular tachyarrhythmia's, the right cardiac nerve is associated with cardiac conduction abnormalities. Stimulation of the amygdala, hippocampus, anterior cingulate gyrus, temporal pole, and subiculum produce cardiac arrhythmias which are independent of the spread of current in the cortex (Anand et al. 1956; Delgado et al. 1960).

In addition stimulation of the hypothalamus increases sympathetic nervous activity and the risk of cardiac arrhythmias (Verrier et al. 2004). Abnormal cardiac sympathetic activation mediated by the central nervous system does not depend only on gross cerebral lesions but also on naturally occurring central events such as occurs in emotional or physical stress. During stress, overwhelming central activation induces arrhythmias and may cause sudden cardiac death from an uncontrolled release of catecholamine (Cannon 2002) which at the cellular level results in the influx of calcium, potassium and magnesium into the cardiac myocytes (Billman et al. 1991). This increases cardiac myocytic contractility and dysfunction, and can precipitate arrhythmias. Lesions of the central nervous system may cause significant electrocardiographic changes and

arrhythmias. Abnormal cardiac rhythms evident on the electrocardiogram are particularly seen in hemorrhagic strokes, subarachnoid haemorrhage and in epilepsy (Cropp et al. 1960; Eisalo et al. 1972; Oppenheimer 1993; Oppenheimer 2006; Oppenheimer 2007). The central nervous system through the modulation of neurohumoral secretion is also critical in regulating cardiovascular autonomic function. In the intact organism adrenergic stimulation causes cardiac sinoatrial depolarization and increased ventricular propensity to develop arrhythmias'. Vagal stimulation however abolishes sinoatrial depolarization, increases ventricular electrical stability and decreases the risk to developing arrhythmias.

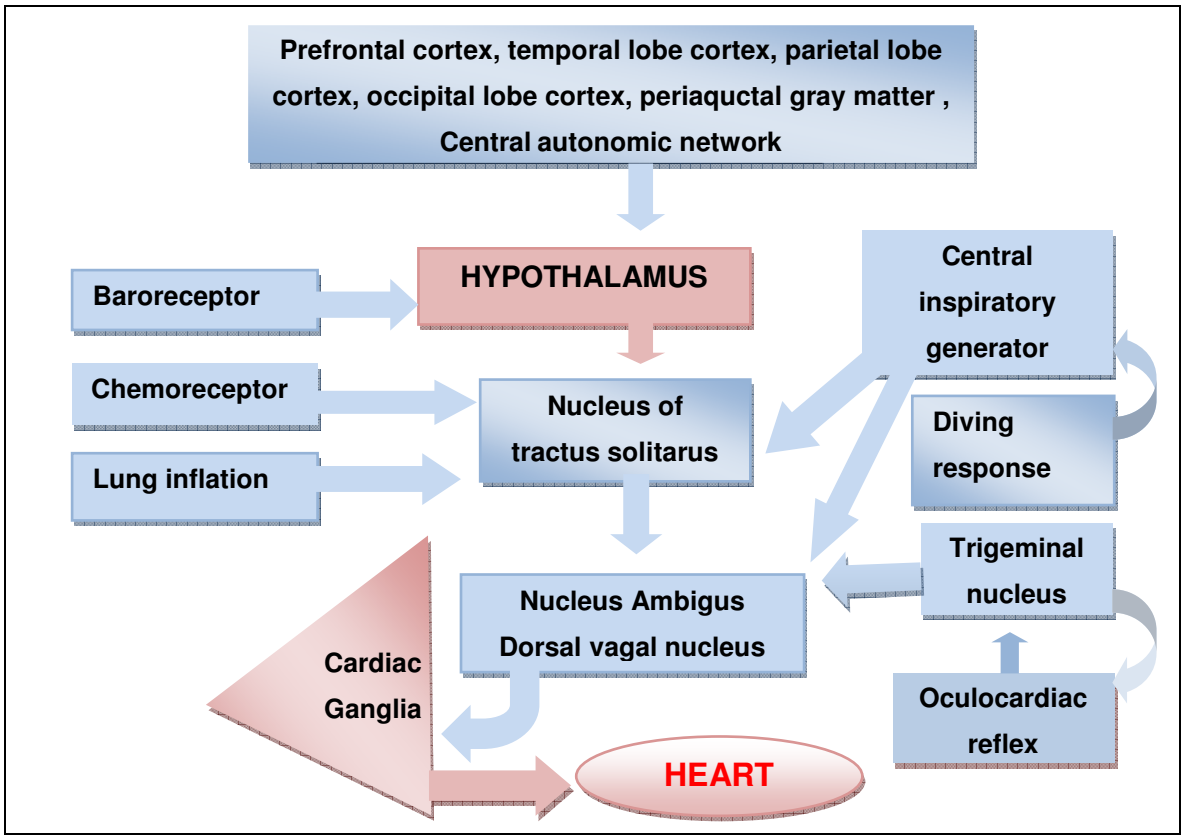


Figure 10 Schematic presentations of central cardiovascular autonomic control. Central oscillators are shown in the midline. Epilepsy excites the cortical components to initiate a series of cardiovascular reflexes.

2.6 Evaluation of autonomic nervous system function

This section describes the various methods that are available to evaluate the autonomic nervous system function. The effective evaluation of the autonomic nervous system depends on an expert medical history and physical examination. There are tests for autonomic function which can be classified as being physiological, neurochemical, pharmacological, imaging and genetical tests. Components of the first two were used to assess autonomic function in this study.

2.6.1 Physiological Tests of Autonomic function

Physiological tests provide reliable methods for detecting abnormalities in the autonomic reflex arcs. The description of these test are beyond the scope of this study and mention will be made of various specific tests with further descriptions of the methods used in this study under the specific sections. Available physiological tests include; The Head up Tilt test, Valsalva manoeuvre, isometric handgrip and cold pressor tests, postural change in heart rate and blood pressure, liquid meal challenge test, exercise testing, carotid sinus massage and the heart rate variability which has been used as non invasive test for the evaluation of cardiovascular autonomic function (Malik 1996).

The heart Rate variability and its measurement

This is a conventionally accepted term used to describe the variations in both the instantaneous heart rate and the normal to normal RR intervals associated with each QRS complex of each successive heart beat using segments of the recorded electrocardiogram. The heart rate variability was first described in 1965 by Hon and Lee when they observed that alterations in interbeat intervals occurred in foetal distress before any meaningful change occurred in the heart rate of the fetus. After about a decade later, Sayers and other group of researchers found the beat to beat heart rate to be a function of other physiologic rhythms particularly respiration and diurnal pattern changes. The association of high risk mortality in the post myocardial infarction period with reduced heart rate variability was first described by Wolf in 1977. By the end of the 1970s, Askelrod had utilized the power spectral analysis to determine heart rate variability which had hitherto been evaluated with only time domain methods. This contributed to the understanding of the autonomic background of the beat to beat

fluctuations in the heart rate recording. It was however, not until the late eighties that the usefulness of the heart rate variability as an independent predictor of cardiovascular mortality in the post myocardial infarction period was established and since then reduced heart rate variability has been reported in several diseases including epilepsy (Adjei et al. 2009; Ansakorpi et al. 2000; Ansakorpi et al. 2002a; Devinsky et al. 1994; Harnod et al. 2009; Malik et al. 1990; Malik et al. 1994; Sathyaprabha et al. 2006). RR interval measurement is a measure of the control mechanisms of the heart rhythm which are determined by activity in the efferent limbs of the cardiac branches of the peripheral autonomic nervous system (Malik 1996).

These two branches are finely tuned and stimulation of the vagal efferent results in suppression of sympathetic efferent activity and vice versa (refer figure 5). The peripheral autonomic activity is intricately synchronous with the cardiac cycle and modulated by the central and peripheral oscillators of the cardiac function. Central oscillators consist of the medullary respiratory and vasomotor centres, whilst the peripheral oscillators are the changes in arterial pressure related to the general state of the individual and respiratory movements. These oscillators generate the rhythmic fluctuations in the efferent autonomic neural discharge to the heart. Analyzing these fluctuating rhythms using the variation in RR interval measurement associated with each heart beat allows inference to be made on the state of the efferent sympathetic and parasympathetic neural activity directed to the heart from the central oscillators to the sinus node.

The standard electrocardiographic equipment is used to acquire raw electrocardiographic data which are digitized by computer programs that detect QRS complexes on a continuous strip of ECG over specified time periods into the RR intervals data. HRV is then calculated from the interval data using two categories of methods: time domain and frequency domain methods. HRV variables determined by time domain methods of HRV are generally simple to calculate. Simple arithmetic variables are the mean RR intervals, mean instantaneous heart rate, difference between day and night heart rates and the difference between the longest and shortest RR intervals. The changes in these variables can be determined secondary to manoeuvres that may result in increased demand on the autonomic nervous system e.g. exercise and valsalva

manoeuvre. Statistical time domain methods are usually done on two types of measurements; 1) direct RR interval measurements and 2) from RR interval differences. The simplest statistical variable to calculate from direct RR interval measurement is the standard deviation of the RR intervals (SDNN). This may be calculated over short or long term period recordings the former allowing one to compare HRV between set time points during various activities (Malik 1996). The standard deviation of the normal to normal RR intervals measures all the components of the heart rate variability. Since standard deviation is a measure of variance, it is arithmetically proportional to the total power of spectral analysis. The variance of a recording is dependent on the recording length and if the recording length increases the variance and SDNN will increase with it. This property of the SDNN makes it inappropriate to compare unequal durations from arbitrarily selected recordings and it is recommended that durations of recordings should be standardized to allow uniform comparison of (SDNN) HRV. In addition to the SDNN other commonly determined statistical parameters using directly derived measurements are 1) standard deviation of the mean RR interval (SDANN) calculated from short 5 minutes periods; 2) average SDNN determined by measuring the SDNN in 5 minute segments of a 24 hour period (SDNN index).

These methods determine changes in heart rate in cycles less or longer than 5 minutes respectively. Using data from RR interval differences, the statistical time domain measures usually calculated are; 1) the square root of the mean squared differences of successive RR intervals (RMSSD); 2) interval differences of successive RR intervals that are greater than 50 milliseconds (NN50); and 3) (pNN50), which is the ratio of NN50 to the total number of RR intervals in a giving segment of ECG. These are measurements of short term variation and they estimate the high frequency components of the heart rate variability (parasympathetic function) (Malik 1996). Frequency domain measures of RR intervals involve performing power spectral analyses. Power spectral density analysis provides useful information on the distribution of variance as a function of frequency. The methods for calculating spectral density may be parametric autoregressive models (least squares method; Yule-Walker method; maximum entropy method) or non parametric (fast Fourier Transformation). The results from both methods are comparable but the main disadvantage of the former over the latter is the need to specify the order of calculation. Three main spectral components are separated in the

frequency spectrum calculated from RR interval segments usually 2-5min recordings; high frequency spectrum (HF) which is a measure of parasympathetic activity, low frequency spectrum (LF) and very low frequency spectrum(VLF) (Malliani et al. 1991). Low frequency power is observed to increase during situations that demand sympathetic activity e.g. head up tilt test at 90° mental stress, and moderate exercise and it is generally accepted as marker of sympathetic activity but this is disputed by some investigators because LF power decrease during these activities but when LF power is measured in normalized units, then it is seen to increase (Malik 1996).

Traditionally HRV has been calculated using 2mins to 24 hour segments of ECG but short 10 seconds segments have been evaluated and found to have similar properties as the longer segments (De Bruyne et al. 1999; Hamilton et al. 2004; Karp et al. 2009; Salahuddin et al. 2007). The main advantage of the latter is the practicality (easier to record and analyze) and the cheap costs involved. There are no convincing disadvantages when compared to the long segment ECG measures. In this study the heart rate variability was measured from 10 second segments mainly because of the above mentioned reasons. Heart rate variability is influenced by a number of factors; 1) Age of individual is inversely proportional to the HRV, the latter showing a linear decline with increasing age. This prevents the use of single normative values in all ages and 2) Timing of testing. There is a well established circadian variation in heart rate variability that is characterized by low HRV during the day especially in the morning hours and increased high HRV at night. In addition to these, other potential confounders which may influence

HRV measures (albeit usually only having a small effect) are hypocapnia, medications with anticholinergic side effects including carbamazepine and body habitus (i.e. weight and height). Body position has also been suggested to influence HRV but the results are conflicting and this is generally not considered an important confounding factor when measuring HRV (Cooke et al. 1998; Ewing et al. 1991; Freeman 2008; Hennessy et al. 2001; Hirsch et al. 1991; Malpas et al. 1990; Ten Harkel et al. 1990; Vallejo et al. 2005).

Heart Rate Variability in Epilepsy

Where epileptic seizures can cause acute autonomic dysfunction such as arrhythmias, chronic changes in epilepsy may lead to chronic autonomic dysfunction and abnormal heart rate response to stimuli. There are published standards of the heart rate variability in cardiovascular diseases (Kamath et al. 1993; Malik et al. 1994; Malik 1996) but the application of heart rate variability in epilepsy and other cerebral disease are still a focus of new research (Flachenecker et al. 1997; Persson et al. 2007a; Tomson et al. 1998). Reduced heart rate variability has been found in previous HRV studies in epilepsy patients (Persson et al. 2007b; Tomson et al. 1998). In epilepsy the clinical significance of the reduced HRV is not entirely clear. However, since it is dependent on an increase in cardiac sympathetic tone, it may be relevant to the pathophysiology of SUDEP (Langan 2000; Langan et al. 2005; Mukherjee et al. 2009). Most HRV studies in epilepsy have been done on interictal ECG. There were none prior to this study in the ictal phase and a few in the peri-ictal phase (Assaf et al. 2008; Toth et al. 2010). In the study of Toth et al (2010), HRV, which was evaluated 20 minutes after the seizure offset was reduced and persisted for as long as 6 hours. This implies epileptic seizures significantly reduce the HRV. It is fashionable to associate increased heart rate during seizure with an automatic reduction in HRV.

However there is no clear correlation between HRV and heart rate and very significant HRV changes can underlie normal heart rates and vice versa (Sztajzel et al. 2008). Given that sudden unexplained death in epilepsy (SUDEP) occurs mainly at night (Langan et al. 2005; Opeskin et al. 2003) and assuming this is associated with night time seizures, then either a nocturnal abnormality of the HRV (Ronkainen et al. 2005) or a seizure related reduction in HRV or both may be related to the mechanism of SUDEP. Knowledge on the influence of epilepsy on circadian rhythms is incomplete. There are some minimal data suggesting that an abnormal HRV circadian rhythm exists in epilepsy and elucidating this could provide useful insights into the mechanisms of SUDEP (Chokroverty 2008). Seizures are unpredictable and the tendency for artefacts to be introduced in simultaneously recorded ECG during seizures has complicated the measurement of HRV changes with seizures. In this thesis, I have used standardised 10seconds ECG

recordings (De Bruyne et al. 1999) to evaluate heart rate variability changes during epileptic seizures and this proved a robust method.

2.6.2 Neurochemical Tests

The measurement of serum concentrations of noradrenalin, adrenalin, noradrenalin/adrenalin response to tyramine and edrophonium, urine catecholamines, plasma renin activity, aldosterone and plasma dihydroxyphenylglycol helps to establish autonomic reflex failure, deficient neurotransmitter release and synthesis, and abnormal target organ responses. Plasma levels of noradrenalin, derived from sympathetic nerve endings that surround arterioles can be used as an index of sympathetic activity however this serum concentration is dynamic and it is affected by several factors including the rate of uptake after release, other endogenous biochemical and postural changes (Schofl et al. 1997). The site of sampling which is usually the antecubital vein may not be suitable for determining norepinephrine activity elsewhere in the body since the local sympathetic discharge at this site will bias the sample result (Bannister et al. 1999). The contribution by adrenal gland to the levels of serum noradrenalin is minimal in the resting state but this increases significantly under conditions of stress and other conditions that cause excess sympathetic discharge including anoxic ischemia associated with generalised epilepsy and the excessive muscular activity of tonic clonic seizures. Circulating adrenaline on the other hand is derived from the chromaffin secreting cells of the adrenal medullar and it is a direct index of the sympathoadrenal axis. This organ is more or less a postganglionic neurone of the sympathetic nervous system. The several other neurochemical tests for evaluating autonomic function are beyond the scope of this project.

Epinephrine and Norepinephrine in Epilepsy

Increase in plasma catecholamine is as a result of the spill over from sympathetic postganglionic nerve endings and the supine measurement is a reflection of the total sympathetic nerve activity. The main aim in determining the levels of these substances in epilepsy is to assess the degree of sympathetic stimulation following seizures rather than to establish sympathetic preganglionic or postganglionic failure. An elevation of noradrenalin and adrenaline after seizures has been demonstrated (Khatun et al. 1997). In epilepsy, the focus on noradrenalin/adrenalin is partly because of their possible involvement in SUDEP through the modulation of cardiovascular autonomic function and

overall sympathetic tone. Cardiac rhythm abnormalities can result from abnormal impulse generation or propagation or both. Abnormal sympathetic stimulation occurring during seizures may cause uncoordinated impulse initiation and propagation and the lowering of the threshold for ventricular fibrillation (Doba et al. 1975; El-Sayed et al. 2007). Beside the described cardiovascular effects, noradrenalin has a role in the control of epilepsy. The anti epileptic mechanism of vagal nerve stimulation and some antiepileptic drugs requires an intact noradrenergic system for their anticonvulsant actions (Giorgi et al. 2004; Schank et al. 2005).

There is some reason to believe that epilepsy itself can affect the urinary excretion of catecholamines. The urinary excretion of dopamine, adrenaline and noradrenalin in epilepsy has been compared to that of their nonepileptic controls. With the exception of dopamine which had lower rates of excretion in epileptic patients, there was no statistical difference for adrenalin and noradrenalin between the two groups. Because dopamine is a precursor during the biosynthesis of noradrenalin and adrenalin, the authors concluded that chronic epilepsy might affect catecholamine synthesis particularly dopamine (Kapustecki et al. 2000).

2.6.3 Pharmacological Tests

These are tests that assess the target organ response to autonomic neurotransmitter release. They may not necessarily determine the receptor integrity or mutations in receptors at the effector organ. Several are available and typical examples are the edrophonium test in myasthenia gravis and intracarvernosal papaverine injections into erectile tissue in patients erectile dysfunction (Goldstein et al. 2007).

2.6.4 Neuroimaging Tests

Several imaging techniques help to visualize the sympathetic innervations of the heart and the autonomic controlled functions of the gastrointestinal system. Barium studies, endoscopy, videoflouroscopy and gastric emptying studies are utilised to evaluate some gastrointestinal autonomic function whilst other imaging studies such as intravenous urography and pelvic ultrasonography can be used in the in the urogenital system. Iodine labelled metaiodobenzylguanidine (MIBG) scintigraphy has been used extensively in the evaluation of sympathetic cardiac dysfunction in the post myocardial infarction period and also in other forms of autonomic failure such as pure autonomic failure,

Parkinson's disease, multisystem atrophy and epilepsy (Druschky et al. 2001). Positron emission tomography (PET) scans after systemic administration of perfusion and sympathoneural imaging agents have helped to evaluate the cardiac autonomic function. This technique has been shown to have good spatial resolution which helps to rapidly visualise the sympathetic innervations of the heart (Goldstein et al. 2007). Recently a group in Germany used methyl-iodo-benzyl guanidine (MIBG) to delineate a cardiac sympathetic dysfunction in epilepsy patients who develop ictal asystole (Kerling et al. 2009).

2.6.5 Genetic Tests

Genetic testing in autonomic evaluation is not readily available but can be used to establish the cause of autonomic dysfunction in conditions like familial amyliodotic polyneuropathy.

Chapter 3

General Methodology and Procedures

This section outlines the general procedures and statistical model used for the whole study. The subsequent results chapters dedicated to each hypothesis will refer to sections in this chapter for description of methodology used. The study was conducted at the Jules Thorn video telemetry unit (Dedicated EEG monitoring unit) in the Department of Clinical and Experimental Epilepsy under the auspices of the National Hospital for Neurology and Neurosurgery, Queen square London.

3.1 Methodology for Literature Review

Data for the review were identified by searches of Pubmed using the following search terms

- “Autonomic symptoms epilepsy ”,
- “Heart rate variability epilepsy and epileptic seizures”,
- “Catecholamines in epilepsy ” ,
- “Serum electrolytes epilepsy”,
- “Cardiac Troponin epilepsy”,
- “Corrected QT interval seizures and epilepsy”.

Only articles in English were selected. No time limit or any other limits were set. I reviewed all the articles identified from the Pubmed searches and selected, from these articles, only those which provided a systematic evaluation of the various autonomic signs and symptoms in epilepsy and during epileptic seizures. Additional data was obtained from selected textbook chapters:

- Epilepsy; A Comprehensive Textbook
- A Clinical guide to Epileptic Syndromes and their Treatment
- Clinical Autonomic Disorders
- The Central Autonomic Network: Functional Organisation and Clinical correlation.

3.2 Subjects

The subjects were recruited from patients who have chronic medically intractable epilepsy which is defined as ; More than two disabling seizures per month, lasting longer than 2 years, and has not been controlled by two or more antiepileptic drugs at their maximum tolerable dose (Radhakrishnan et al. 1998). All subjects were studied during their admission for video EEG telemetry at the National Hospital for Neurology and Neurosurgery and unless otherwise indicated all patients had extra cranial video EEG monitoring. Research ethics approval was provided by the National Hospital for Neurology and Neurosurgery research ethics committee and strict adherence to the principles of clinical research was adhered to. The study was in three parts each addressing one of the specific aims. Informed consent (Appendix 9.1a and 9.1b) was sought from all willing participants who satisfied both inclusion and exclusion criteria.

The principal inclusion criteria were:

- Patients with epilepsy admitted for localization and characterization of their seizures at the video−EEG telemetry unit of the National Hospital for Neurology and Neurosurgery
- Age range 18 to 65 years
- Ability to give informed consent
- No co morbidities such as diabetes mellitus, hypertension and no documented evidence of autonomic nervous system dysfunction.

And the exclusion criteria were:

- Patients without epilepsy including pseudoseizures
- Unconscious and very ill patients
- Mentally insufficient patients or psychological disease patients such as schizophrenia who were not able to give informed consent.
- History of diabetes mellitus, hypertension or any autonomic nervous system abnormality.
- History of myocardial infarction.
- History of type I and type II pulmonary disease.

Gender, race and ethnicity of participants did not affect inclusion or exclusion from this study. Overall a total of 207 patients (191 in HRV Study and 16 patients in the Electrolyte study) were included in this project. The number of participants for each part of the study was derived using power calculations based on conventional size estimate using a standard of power of 80% and significance level of 0.05. All the patients satisfied the inclusion criteria described above, and underwent greater than 92 hours of continuous EEG and ECG monitoring. Up to 40 participants were excluded from the study because there were no recorded seizures during the period of admission or the seizures recorded on admission were found to be non epileptic episodes.

3.3 Methodology for Heart Rate Variability Studies

There were three time periods of interest used in evaluating the HRV for the first hypothesis;

- The immediate pre-seizure period – within 20 seconds before the onset of both clinical and EEG seizure
- The ictal period – the period of the electrographic seizure activity corresponding to precisely the midsection of the discharge.
- The immediate postictal period – 20 seconds after the cessation of the electrographic discharge.

ECG was standardized for uniform comparison of HRV by using 10 second segments of ECG recordings (Karp et al. 2009; Salahuddin et al. 2007). These segments were free of artefacts. ECGs corresponding to the first three ictal seizures for each subject were analysed.

To test the second hypothesis, 24 hour day period was equally divided into 12 hour blocks from 20:00 pm to 07:59am, and from 08:00am to 19:59pm, representing night time and day time respectively. Five minute segment of ECG at the beginning of each hour was used to represent and evaluate the hourly HRV in each patient.

Electrophysiology data acquisition

Electroencephalograph (EEG) were mainly acquired using scalp electrodes which were placed according to the 10-20 system in almost all patients with additional special electrodes (10-10 system and sphenoidal electrodes) being used in specified patients. For patients who had intracranial studies (n=26), the electrodes which were subdural grids, subdural strips and depth were inserted stereotactically under general anaesthesia by the neurosurgical team. Up to 64 channels of EEG including superficial sphenoidal electrodes were recorded. Disposable Ag/AgCl EEG electrodes were used for all extracranial recordings. Commercially available skin preparation gel (Nuprep ECG/EEG abrasive skin prep GEL, D.O Weaver &Co) and electrolyte gel (Redux®Gel, Parker Lab Inc) were used to prepare the scalp electrodes which were then secured with porous adhesive tape. Electrodes were routinely checked and electrode gel reapplied to maintain electrode impedance at less than 5 kohm. Amplifier settings were: Filters set at 0.5Hz LFF and 70Hz HFF; Recording sensitivity set at 7μV and sampling rate of greater then 250Hz in all channels including the ECG channel. Activation methods used were mainly antiepileptic drug withdrawal and in some cases sleep deprivation.

Electrocardiograph (ECG) was recorded using two disposable skin contact adhesive electrodes attached to the chest on each side below the clavicle and connected to the Nicolet One digital recording amplifier (The Modified Lead I ECG). Amplifier was set similar to the EEG acquisition channels. 2 channels of ECG were recorded using this modification. The sampling rate for the ECG signal was 256 Hz. Because ECG and EEG were recorded simultaneously I was able to accurately correlate the ictal EEG onset and clinical onset with the ECG. Video was recorded using NicOne LTM systems (VIASYS Healthcare Inc, Madison Wisconsin) which had motion sensor detectors for night time video recordings.

RR Interval Analysis and Computer programs Used

The ECG/EEG recordings once acquired were stored on data CDs and reviewed using Nicvue systems (Modular Neurodiagnostic Software system, version 5.3, registered to VIASYS Health Care™). In the peri-ictal heart rate variability study video recordings and EEG for all recorded seizures were reviewed simultaneously. For purposes of localization and classification, seizures were viewed in more than one montage; mainly “the

montage in which it was recorded" (referential) and bipolar "double banana" montage. Electrographic seizure duration was noted by marking the start and end time, and correlated with the video recording to rule out non epileptic events. The seizure was then equally divided into 3 time segments based on the duration of the electrographic discharge; thus there was an initial section of seizure, mid section of seizure and late section of seizure that was close to the termination of electrographic activity. Ten seconds of the ECG/EEG signal in the midsection was selected to represent the ictal time period. After identifying the ictal period, 10 seconds of ECG/EEG signal were identified in a time period, 20 seconds after the end of electrographic discharge and in the period just before the onset of electrographic discharge to represent the "postictal" and "preictal" time periods respectively.

In the diurnal heart rate variability study, ECG in the interictal period was reviewed from the onset of telemetry monitoring till 24hrs afterwards. 5 minute durations of ECG were analysed taken from the beginning of every hour for 24 hours, starting from the onset of investigation. These sections were generally devoid of movement artefacts. All ECG/EEG signal data were acquired in EDF (*European Data Format*) and underwent further computer digitization of the ECG signal to eventually sequence the RR intervals (Figure 11, 12 and 13). This process was done for all patients. After exporting data in EDF, a custom made software(*EDF to ASCII Converter,* figure 13) was then used to manually select only the ECG signal channel at sampling rate 256 Hz from the complete data set and converted into an ASCII(American standard code for Information Interchange) format file. A second custom made software (*ECG_Analysis_32 program*), consisting of a programme which utilizes an amplitude threshold applied to a channel of selected ECG (bandwidth 10Hz to 20Hz, sampling rate 256Hz) in ASCII format to detect QRS complexes, was used. Using the same software, The ECG signal marked with QRS complex detections, was then reviewed visually, spurious detections were removed and missed detections inserted manually for every segment of ECG analysed. This method of measuring RR intervals has been recommended by the HRV task force because manual editing of RR intervals as opposed to automatic filter editing, which tends to exclude RR intervals differing by more than 20% from the previous RR interval, is highly accurate and leads to minimal errors in the RR interval analysis. Also the RR interval analysis done

at a sampling rate greater than 250 Hz was in accordance with the HRV task force recommendations (Malik 1996).

The time domain parameters; mean instantaneous heart rate (mHR), square root of the mean squared differences of successive RR intervals (rMSSD) and standard deviation of RR intervals (SDNN) were determined for each segment of ECG analyzed using Microsoft Excel. Instantaneous heart rate was determined for each segment by mathematically dividing 60 by the numerical value of each successive RR interval measured in seconds to obtain the heart rate in beats per minute. SDNN is a measure of variance of the whole segment and thus reflects all the cyclic components responsible for heart rate variability A reduced SDNN is a sign for increased cardiac sympathetic tone (Riediker et al. 2005). Frequency domain analysis was carried out on the 5 minute ECG segments using a custom made software that utilised mathematical fast Fourier transformation to separate the signal into its component power spectra (low frequency =0.04-0.15 and high frequency =0.15-0.40) (see figure 12) and automatically determines the ratio of low frequency power to high frequency power. This ratio has been described to be a measure of the cardiac sympathetic/vagal balance (Malik 1996). Only the mean heart rate and sdnn were computed on the short 10 seconds segments whilst all HRV indices mentioned above were computed on the longer 5 minute segments.

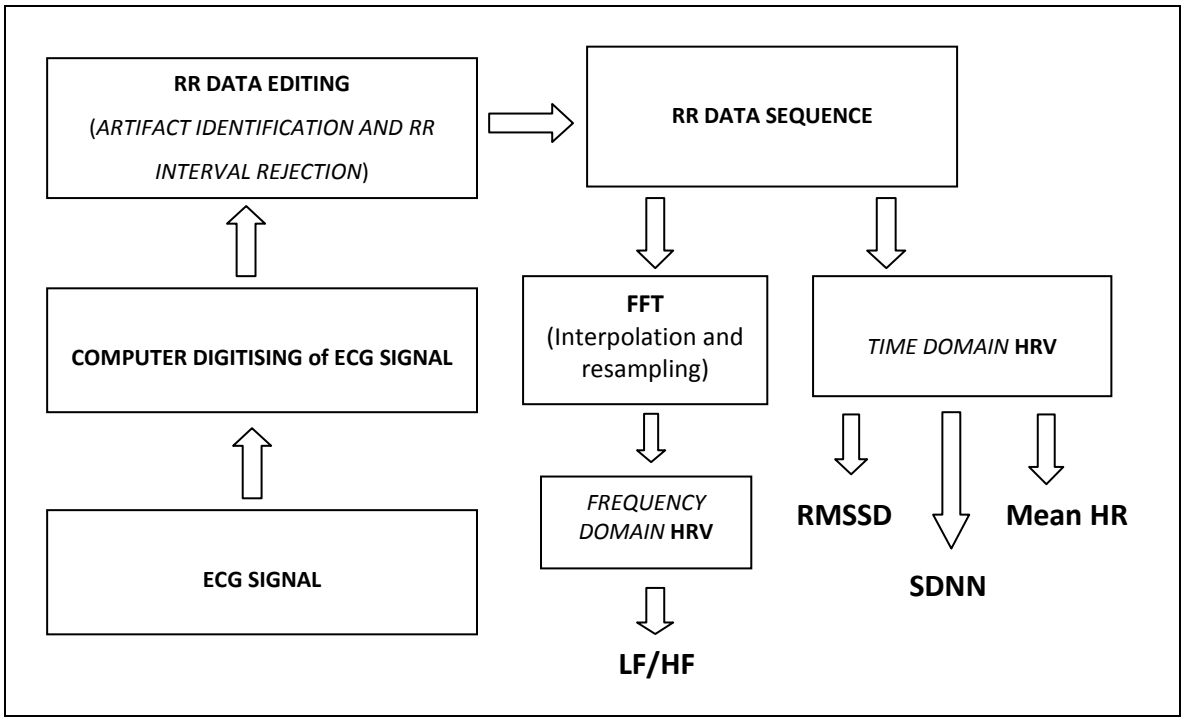


Figure 11 Flow diagrams that summarize the steps used in processing raw ECG signal to obtain data for HRV analysis. The ECG signal is extracted and by series of computer software processes the signal is digitised then the RR series manually edited before being converted to time frequency domain measures. RR data editing signifies the series of events that is mentioned in figure 13. SDNN standard deviation of RR intervals; RMSSD square root of the mean squared RR interval difference; mHR mean heart rate; LF low frequency power; HF high frequency power.

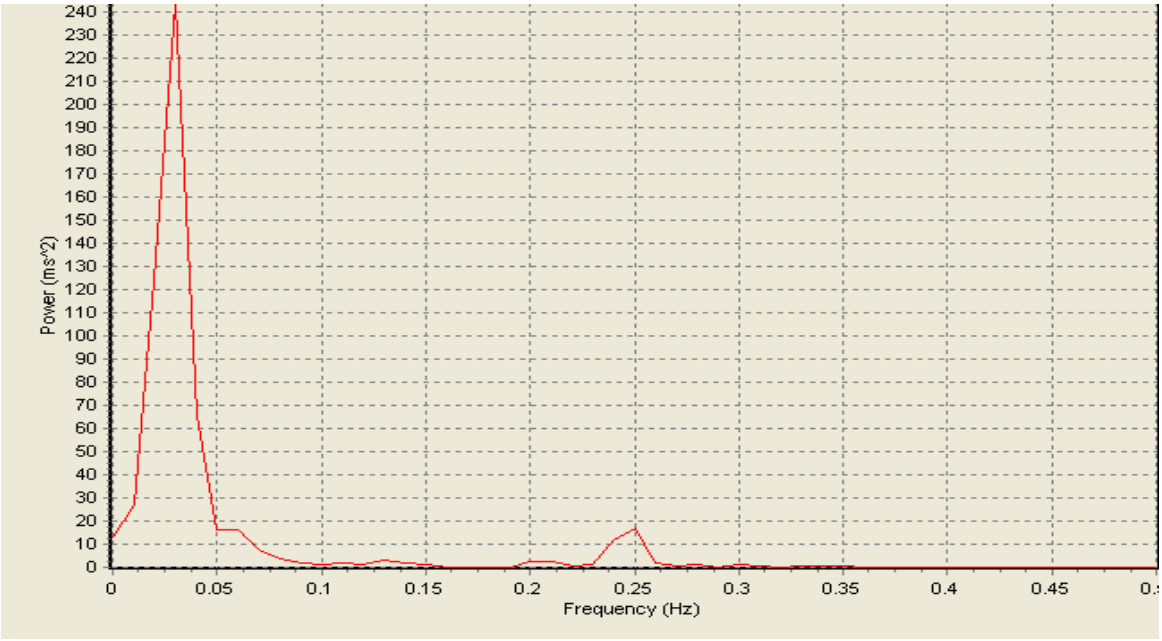
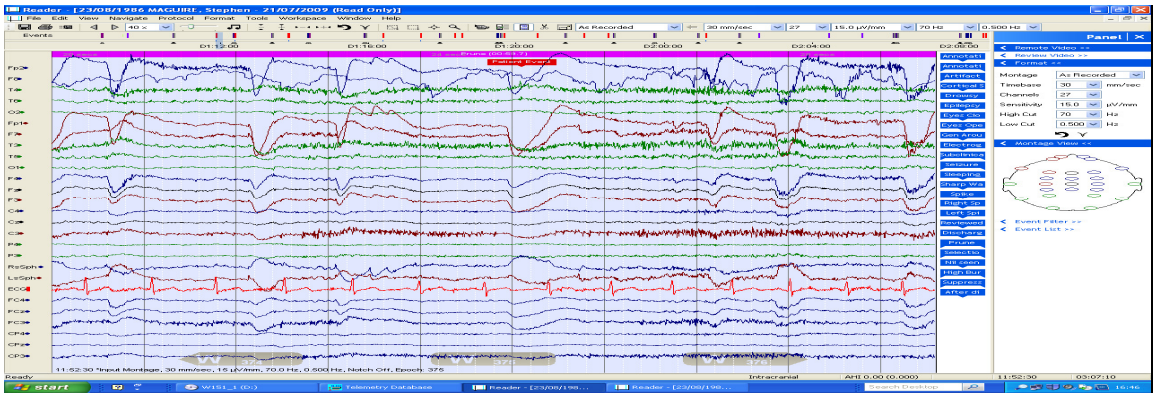
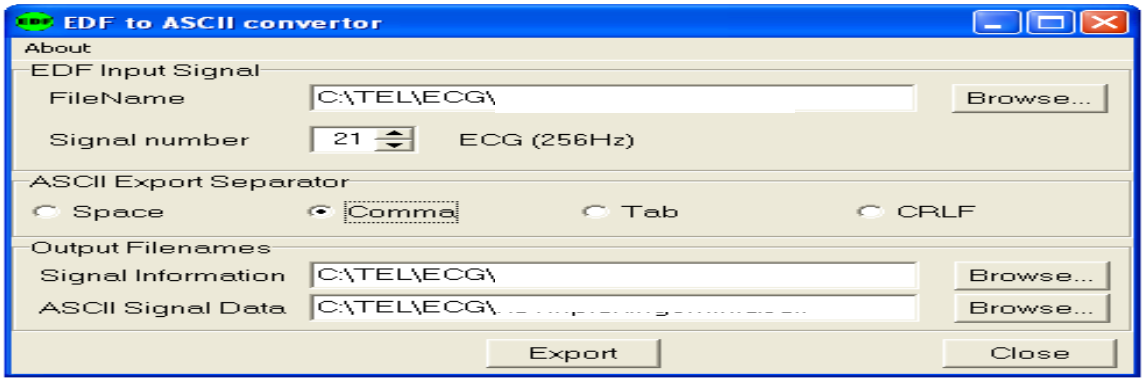


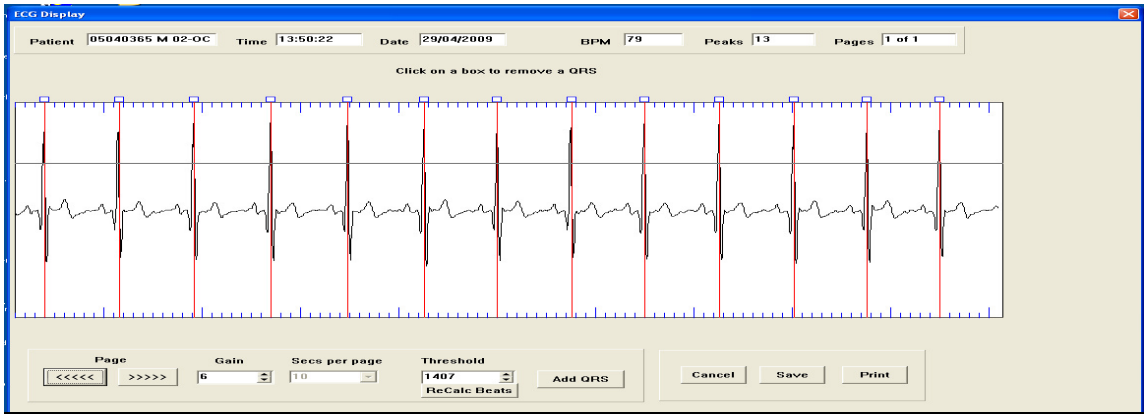
Figure 12 Graphical display of power spectral analysis from a section of ECG used in the study. Two spectra are seen in which the larger spectrum corresponds to the low frequency band (0.04-0.15) and the smaller spectrum corresponds to the high frequency power (0.15-0.40). The area under the curve in each peak is the corresponding power and this is estimated by integrating between frequency limits.



Step 1 EEG and ECG are run in Nicvue review systems and data corresponding to time of interest is selected to be analyzed by the ASCII converter. ECG signal appears in bright red.



Step 2 This programme manually selects the ECG signal converts to ASCII data from EDF.



Step 3 *ECG_ Analysis 32 programs* detects QRS complexes and measures RR intervals by applying an amplitude threshold to a single channel of filtered ECG (sample rate 256Hz). The ECG signal, marked with QRS complex detections (vertical red lines), are then visually inspected, and spurious detections are removed whilst missed detections inserted manually.

Figure 13 Computer programs involved in the stepwise digitization of raw electrophysiological data (ECG) for the analysis of RR intervals. Apart from the Nicvue software used for reviewing the raw EEG/ECG data, other software's were required to extract and analyze the RR intervals as shown in this diagram.

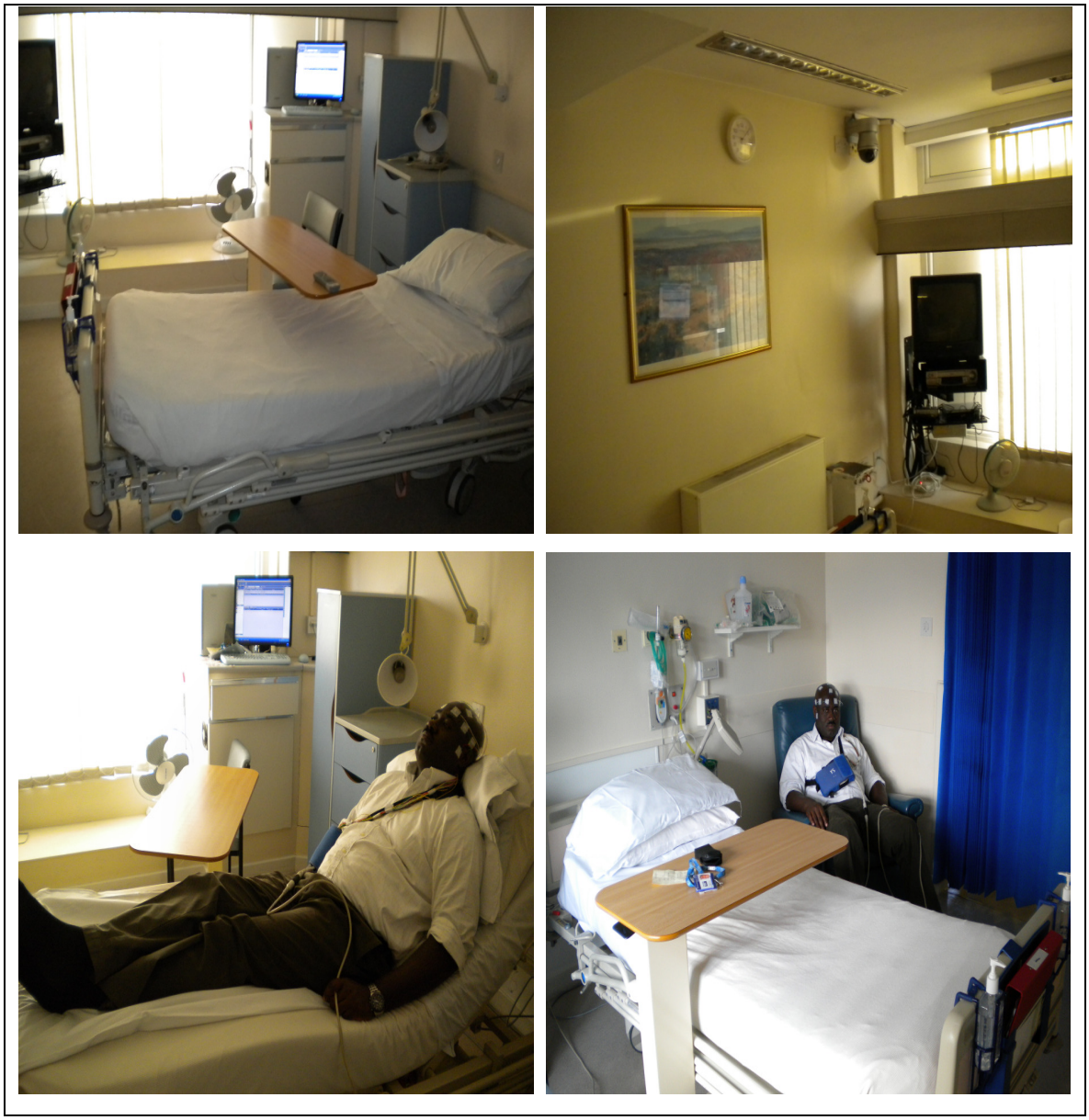


Figure 14 A picture of the very relaxed atmosphere of a typical investigation cubicle at the Sir Jules Thorn Video Telemetry Ward in the National Hospital for Neurology and Neurosurgery. On screen display of recordings and the video camera are displayed in the top pictures. Recording Amplifier (Blue box) is strung across investigator. Electrodes have been placed in a typical 10-20 electrode placement system in a longitudinal double banana montage on the investigator. White patches are the cut pieces of porous adhesive tape used to secure the electrodes. This was done for all patients and has been described in the text. Courtesy: Sir Jules Thorn Video Telemetry Unit, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG.

3.4 Catecholamines, Serum Electrolytes and Cardiac Enzymes

Peri-ictal measurements for serum catecholamines, electrolytes and the QT time were made for patients with medically intractable epilepsy who had complex partial seizures and also those who had secondary generalization during presurgical video-telemetry evaluations. Only those patients who had obvious clinical seizures, (Secondarily generalised tonic clonic seizures and complex partial seizures) correlated by video recording were included in this study.

Catecholamine and Electrolyte estimation

Blood samples were taken at 3 different time points

- Within 5 minutes after an observable seizure for catecholamine estimation
- 12 hours after the seizure to measure change in Troponin.
- At the end of recording, on the morning of discharge from the ward for patients who had blood withdrawn immediately after observed seizures.

The rationale for choosing these time periods for this study were: 1) Adrenalin/ Noradrenalin when released are rapidly hydrolysed from the blood stream within 10 minutes (Goldstein et al. 2007) through various biochemical processes and any time beyond this would have missed crucial peaks in the plasma levels. 2) Serum markers of myocytic damage (Troponin T&I), begin to rise 3-4 hours after onset of ischemia and peaks in plasma after 12 hours persisting for up to 14 days. 3) Withdrawing baseline samples at the onset of recording when no seizures had been ascertained, could have led to discarding and wastage of human tissue in the situation where no seizures occurred during the investigation or if the 5 minute benchmark was missed.

Ten mls Venous blood was obtained from the antecubital fossa using 21G sterile Terumo needle syringes under aseptic conditions and separated into two plastic SST gel (Serum Separating Tube, silica gel)containing blood collection tube and labelled for electrolyte and catecholamine analysis for each patient accordingly. Each arm was used interchangeably. By virtue of study design, all the patients had seizures on different time of day and week, allowing for the crucial 5 minute post seizure sample to be taken with minimal time bias. The first SST gel bottle, containing 5 mls of venous blood for

determination of the electrolytes; Na^+, K^+, Ca^{2+}, Mg^{2+} and the serum cardiac myocytic damage marker; Troponin T and I, was immediately sent for laboratory analysis to reduce risk of autolysis' of red blood cells which is likely to affect potassium (K^+) plasma estimations. To prevent and reduce catecholamine decay, 0.1 mls of the catecholamine preservative EGTA-Glutathione was added to the second sample bottle containing the other 5 mls of whole venous blood earmarked for catecholamine estimation and the bottle tipped over gently to ensure adequate mixing of preservative and sample, and activation of the anticoagulant. The sample was then spun in refrigerated centrifuge at 4°c and speed of 1800rpm for 12 minutes. The plasma was then separated into a clean sample tube and immediately frozen in a minus 70 degrees celsius industrial freezer before being sent for estimation of catecholamines. Catecholamine measurement was done in collaboration with the Autonomic unit of the National Hospital for Neurology and Neurosurgery. The catecholamines were expressed in units of pg/ml, electrolytes expressed as mmol/L and Troponin, ug/L. Calcium was estimated as corrected calcium after adjusting for serum albumin. In addition, peri-ictal QT interval was determined from the period before the seizure; and 5 minutes after the seizure. Interaction between QT interval electrolytes and catecholamine levels at the base line and 5 minutes post seizure time points was evaluated. QT interval was manually measured with callipers from the start of the Q wave to the end of the T wave on the modified lead one ECG for three successive beats within the time periods. RR intervals for these successive beats were determined and used to calculate the corrected QT using Bazetts formula [$QTc = QT*(RR)^{-1/2}$](Luo et al. 2004).

3.5 Additional Sources of Data

Age, gender and duration of epilepsy were obtained from the patient records using computerized hospital database and patient notes for all subjects. In addition the yearly seizure frequency and the antiepileptic drug polytherapy in which carbamazepine was inclusive at the time of telemetry were determined. Duration of epilepsy was determined as the years of uncontrolled epilepsy from the time of confirmation of epilepsy diagnosis to time of telemetry i.e. when patients were consented for this study. For purposes of statistical analysis lobar localisation were grouped into temporal and extratemporal lobe epilepsy.

3.6 Statistical Analysis

Multilevel model analysis has been used to analyse the data in this study using STATA 10 intercooled statistical software programme (StataCorp LP, Texas 77845, USA) registered to the UCL:

- To test the primary hypothesis, comparisons of heart rate variability were made in the time periods: before; during and after a seizure and the effects of hemispheric laterality of seizure and lobar location were adjusted on the response variable which in this case was the difference in time points; before during and after. This statistical analysis was done using linear mixed model analysis, a multilevel mixed linear regression analysis, which allows within individual and between individuals' variation to be accounted for and makes straight forward adjustment for the predictions of the effects of the explanatory variables: seizure duration, hemispheric and lobar location, age and epilepsy duration on the response variable. All outcome variables were tested for normality by using normal plots after transforming the data within each patient to have a zero mean and unit variance. For inclusion in the multiple regression models all the explanatory variables were first considered one at a time using univariate analysis to select the confounders with the highest association to the various response variables, i.e. p value less than 1. The final models have been presented in the chapters 4 and 5 of this thesis. Population averaged models were fitted in Stata 10 using linear mixed model analysis with the xtmixed command.

- To test the second hypothesis, four summary statistics were produced for each outcome variable: rMSSD, sdnn, mHR, and LF/HF. The data was multilevel in structure with time points nested within patient. The four outcome variables were tested for normality by using normal plots after transforming the data within each patient to have a zero mean and unit variance. The variable LF/HF was extremely skewed to the left and a log transformation was applied. It should be noted that back transformation of a mean on the log scale results in a geometric mean on the original scale. Each of the four outcome variable was

plotted against the 24hour time period to show the diurnal pattern graphically. Explanatory variables considered at the patient level were age, sex, number of years since diagnosis, number of seizures per year, Antiepileptic drug polytherapy with carbamazepine, location and laterality of the seizure focus. The explanatory variable at the time point level was whether the reading was taken between 8 am to 7pm (day) or 8pm to 7 am (night). First single variable models and then multivariable models were fitted to the data. In order to take account of data collected sequentially over time the within patient correlation structure was assumed to be autoregressive of order one. Two way interactions between the variables were investigated and the models were re-parameterized to investigate any significant interactions found. Population averaged models were fitted in Stata 10 using generalized estimating equations with the xtgee command. The final models for each outcome are presented in chapter 5 of this thesis.

- To test the third hypothesis, sodium, potassium, calcium, magnesium, noradrenalin and adrenaline levels results were obtained from 16 patients. The corrected QT interval (QT_c) was recorded from electrocardiogram (ECG) traces before seizure and 5 minutes after the seizure. All outcomes were tested for normality by using normal plots and no transformations were required. The data were analyzed for each electrolyte separately with multilevel mixed effects linear regression in Stata 10 with the xtmixed command. An initial analysis included the time the recordings were taken as a categorical fixed effect and patient as a random effect. The results was declared statistically significant at the 5% level and the before seizure level was used as the baseline category for comparison. Seizure duration and the seizure type were included in a secondary multivariable analysis as explanatory variables at the patient level. These analyses are presented in chapter 6 of this thesis.

These statistical methods were recommended by Dr Constantinos Kallis and Mrs Pauline Rogers, statisticians at the Institute of Neurology, who instructed me in the planning and application of the statistical methods.

Chapter 4

Heart rate variability during subclinical seizures in partial epilepsy

Subclinical seizures are defined as electroencephalographic seizure patterns without any disturbance of motor, sensory and conscious functions in the awake patient and without any movement or arousal in the sleep patient (Zangaladze et al. 2008). They must not be confused with subclinical rhythmic electrographic discharge of adults which is a rare monophasic sharply contoured theta frequency discharge, usually diffuse but with temporal lobe dominance and occurs in the drowsy or restful awake individual also with no associated clinical symptoms as well. The defining feature of the latter is the "state restriction", lack of post ictal slowing and preservation of posterior dominant rhythms. Long term video monitoring in epilepsy provides means by which subclinical seizures can be observed and studied. Subclinical seizures are closely related to the clinical seizures itself and may be indicative of the location of the epileptogenic zone. The lack of clinical symptoms during subclinical seizures is probably due to insufficient propagation or synchrony of the electrographic discharges (Zangaladze et al. 2008). I have used the above definition, although there is a "grey area" between the terms "subclinical" and "clinical" and with the use of more sophisticated neurological testing, it is possible that subtle movements and cognitive dysfunction may be detected during these electrographic discharges. Moreover, it is well recognised that even interictal epileptiform discharges can produce subtle impairment of cognition (Binnie 2003). It should be noted that in this study patients with spike wave discharges in Idiopathic Generalised Epilepsy were not included and the results obtained in partial epilepsy may well not apply in other forms of epilepsy.

4.1 Aim

The aim in this study was to test the hypotheses that changes in heart rate variability (HRV, as an index of cardiac autonomic function) occur in partial epilepsy without clinically overt seizures, (i.e. during subclinical electrographic seizure patterns), and that changes observed can help localise or lateralise the seizure discharge focus.

4.2 Methodology

Only patients who had intracranial video EEG were recruited for this study. The electrodes which were either 64 contact subdural grids or10 contact subdural strips or 6 contact depth had been inserted stereotactically under general anaesthesia. Details discussed in Chapter 3, section 3.3.

4.3 Statistical Analysis

Ictal and postictal HRV were compared with the preictal HRV (baseline) using linear mixed model analysis. Details discussed in chapter 3 sections 3.6.

4.4 Results

Summary of Clinical features

26 patients with medically refractory partial epilepsy were included in this study. One TLE patient without underlying cardiac disease had had an episode of ictal asystole in previous video-EEG telemetry, and a DDDR cardiac pacemaker had been implanted. A total of 74 subclinical seizures (2-3 per patient) were analysed. Twelve patients displayed left hemisphere subclinical seizures (7 patients TLE, 5 patients FLE) and 14 patients' right hemisphere subclinical seizures 7 TLE, 7 FLE). The mean (SD) duration of subclinical seizures was 72(14) s (range 10 - 964 s). The most common neuropathological finding was hippocampal sclerosis (Table 4.1). The subclinical events were highly localised electroencephalographically with minimal spread to adjacent contacts of respective electrodes or grids (Table 4.2). Table 4.3 shows the overall data in the three time periods, whilst tables 4.4 and 4.5 depict HRV in temporal and frontal lobes respectively.

Table 4.1 Summary of the clinical features of patients (n=26)

Clinical characteristics	Observation
Duration of epilepsy mean(SD) (range) years	28(12)(7-47)
Duration of Subclinical Seizures mean(SD)(range) s	72(14)(10-964)
Age mean(SD)(range) years	38(10)(21-54)
Gender	13 males 13 females
Aetiology of seizures	9 HS 1FCD 3 Tumours 3 Trauma 9 Cryptogenic
Epilepsy Type	14 TLE 12 FLE
Total number of subclinical seizures	74

TLE temporal lobe epilepsy; FLE frontal lobe epilepsy; HS hippocampal sclerosis; FCD; focal cortical dysplasia; S; seconds.

Table 4.2 Electrode placement and type, Total number of Electrode contacts and the total number of contacts involved during spread.

Patient	Lesion type	Intracranial Electrode type	Total Number of Electrode contacts	No of contacts involved during spread
1	Hippocampal sclerosis	Depth and Subdural strip	40 (20 left, 20right)	3
2	Hippocampal sclerosis	Depth, Subdural grid and strip	44	7
3	Hippocampal sclerosis	Depth, Subdural grid and strip	38	6
4	Hippocampal sclerosis	Depth, Subdural grid and strip	68	14
5	Hippocampal sclerosis	Subdural strip	12 (6 left, 6 right)	3
6	-	Depth, Subdural grid and strip	66	3
7	Hippocampal sclerosis	Subdural grid and strip	48	4
8	Hippocampal sclerosis	Depth and Subdural grid	24(12 left, 12 right)	6
9	Trauma (contusion)	Subdural grid	12	3
10	Hippocampal sclerosis	Subdural grid	30 (18 right, 12 left)	4
11	Hippocampal sclerosis	Depth and Subdural grid	30(18 right, 12 left)	1
12	Focal cortical dysplasia	Subdural grid and strip	50	1
13	Hippocampal sclerosis	Depth and Subdural grid	24(12 left, 12 right)	2
14	Hippocampal sclerosis	Subdural grid and strip	30(18 right, 12 left)	4
15	DNET(WHO G1)	Depth and Subdural strip	54	6
16	Rasmussen Encephalitis	Depth and Subdural strip	48	16
17	-	Depth and Subdural strip	48	7
18	-	Subdural grid and strip	60	11
19	-	Depth and Subdural strip	66	2
20	Focal cortical dysplasia	Depth, Subdural grid and strip	58	1
21	-	Depth and Subdural strip	70	6
22	Cavernous hemangioma	Depth, Subdural grid and strip	60	14
23	Oligodendroglioma	Depth and Subdural strip	54	10
24	Frontal lobe cystic lesion	Depth and Subdural strip	40	9
25	-	Depth, Subdural grid and strip	54	12
26	-	Depth, Subdural grid and strip	56	10

Electrode placements, Electrode type and the contacts involved in spread. The seizures remain highly localised as can be seen from the number of electrode contacts involved in spread. RFL right frontal lobe; LTL left temporal lobe; RTL right temporal lobe; LFL left frontal lobe.

Table 4.3 Comparison of sdnn and mHR in the 3 time periods in all patients

	Variables	Time1 (Before Seizure) Mean (SD) range	Time 2 (During Seizure) Mean (SD) range	Time 3 (After Seizure) Mean (SD) range
Sdnn	overall	28.41(20.26)*2.73-83.23*	27.32(16.57)*1.83-64.12*	29.30(21.23)*2.31-87.97*
	between	(17.57)*3.43-70.93*	(14.63)*2.86-51.07*	(20.29)*3.18-70.94*
	within	(10.63)*3.59-64.61*	(8.45) *8.91-50.22*	(8.09)*12.09-54.51*
mHR	overall	80(10)*63-108*	82(11)*61-105*	81(10)*65-100*
	between	(10)63-100	(10)*63-99*	(9)*66-98*
	within	(4)*72-94*	(4)*65-101*	(4)*72-94*

Table shows overall mean and standard deviation in addition to the between and within patient standard deviations. Within patient variation is low compared to between patient variation. Sdnn standard deviation of normal to normal RR intervals; mHR mean instantaneous heart rate; Seizure subclinical seizure; Italicised figures represent the range and the figures in brackets' are the standard deviations.

Table 4.4 Comparison of sdnn and mHR in temporal lobe epilepsy

	variables	Left hemisphere mean(SD) range	Right hemisphere mean(SD) range
sdnn/ms	overall	12.79(5.99)*3.08-27.39*	34.47(17.08)*6.9-87.97*
	between	(3.97)*7.24-18.31*	12.34)*25.02-59.61*
	within	(4.56)*3.34-27.58*	(13.43)*13.74-67.86*
mHR/bpm	overall	90(9)*68-108*	78(6)*66-90*
	between	(7)*79-99*	(5)*72-85*
	within	(5)*75-101*	(4)*68-87*

Table shows overall mean and standard deviation in addition to the between and within patient standard deviations. There is lower within patient variation as compared to between patient variations. Sdnn and mHR values recorded from the left are lower than the right. Sdnn: standard deviation of normal to normal RR intervals, mHR: mean instantaneous heart rate. Italicised figures represent the range and the figures in brackets' are the standard deviations

Table 4.5 Comparison of sdnn and mHR in frontal lobe epilepsy

	variables	Left hemisphere mean(SD) range	Right hemisphere mean(SD) range
sdnn/ms	overall	38.39(20.73)*5.50-85.41*	29.67(20.18)*1.83-79.14*
	between	(19.84)*11.21-63.18*	(16.38)*3.16-42.09*
	within	(10.37)*8.32-61.73*	(13.18)*1.29-71.68*
mHR/bpm	overall	78(10)*64-96*	78(11)*61-100*
	between	(10)*67-94*	(9)*64-93*
	within	(3)*72-83*	(6)*67-102*

The difference is not significant between left and the right side: sdnn (P=0.42), mHR (P=0.90). Sdnn: standard deviation of normal to normal RR intervals, mHR: mean instantaneous heart rate. Italicised figures represent the range and the figures in brackets' are the standard deviations

Sdnn during subclinical seizures

On average, there is no significant change in HRV from preictal to ictal (P= 0.57) and between the preictal and postictal HRV (P=0.64). After adjusting for all the other variables, HRV is lower by 27ms in patients with temporal lobe epilepsy (P=0.003, 95%CI 9.37ms to 45.39ms). Within patients with temporal lobe epilepsy, Right hemispheric epileptogenic region increases the HRV by about 24ms (P=0.001, 95%CI 9.91ms to 37.96ms). The effects of age (P=0.067), gender (P=0.68), duration of seizures (P= 0.17), number of seizures (P=0.27) and spread to adjacent brain regions (P=0.27) on the HRV during subclinical seizures are not statistically significant.

Table 4.6 Results of sdnn analysis

Sdnn/ms	coefficient	standard error	P value	95% CI
Time period1(preictal vs. ictal	-1.09	1.93	0.57	-4.87 to 2.69
Time period2(preictal vs. postictal)	0.89	1.93	0.64	-2.88 to 4.67
Gender(female vs. males)	2.35	5.77	0.68	-8.95 to 13.67
seizure duration/secs	0.01	0.009	0.17	-0.005 to 0.03
epilepsy duration/years	0.25	0.22	0.26	-0.18 to 0.69
Age/years	-0.59	0.32	0.067	-1.23 to 0.04
Lobar location(TLE vs. FLE)	-27.38	9.18	0.003	-45.39 to -9.37
TLE (Right vs. Left)	23.94	7.15	0.001	9.91 to 37.96
FLE(Right vs. Left)	-6.34	7.89	0.42	-21 to 9.12
Spread to adjacent contacts	-0.75	0.68	0.27	-2.08 to 0.58
Seizures	1.15	1.04	0.27	-0.91 to 3.21

A negative coefficient means the outcome variable decreases by that amount when the explanatory variable is adjusted for. FLE: frontal lobe epilepsy, TLE: temporal lobe epilepsy.

Mean heart rate during subclinical seizures

On average, mean instantaneous heart rate increases during subclinical events by about 2bpm (P= 0.023, 95% CI 0.24bpm to 3bpm) after adjusting for all the other variables. Overall the rise in mean heart rate is higher in patients with temporal lobe epilepsy compared to those with frontal lobe epilepsy by about 15bpm (P=0.016, 95% CI 3bpm to 27bpm) after adjusting for the effects of all the other variables. Within the patients with temporal lobe epilepsy, right hemispheric epileptogenic region decreases the mean heart rate by about 11bpm (P=0.026, 95%CI 1bpm to 20bpm). The effects of age (P=0.85), gender (P=0.79), seizure duration (P=0.52), epilepsy duration (P=0.38), spread

to adjacent brain regions (P=0.34) and the number of successive seizures (P=0.09) on the mean heart rate during subclinical seizures are not significant.

Table 4.7 Results of MHR analysis

mHR/bpm	coefficient	standard error	P value	95% CI
Time period1(preictal vs. ictal	2	1	0.023	0.24 to 3
Time period2(preictal vs. postictal)	1	1	0.15	-0.4 to 3
Gender(female vs. males)	-1	4	0.79	-9 to 7
seizures	-1	0.42	0.09	-2 to 0.4
seizure duration/secs	-0.003	0.004	0.52	-0.01 to 0.005
epilepsy duration/years	-0.13	0.15	0.38	-0.43 to 0.16
Age/years	0.04	0.22	0.85	-0.4 to 0.5
Lobar location(TLE vs. FLE)	15	6	0.016	3 to 27
TLE (Right vs. Left)	-11	5	0.026	-20 to -1
FLE (Left vs. Right)	0.64	5	0.90	-10 to 11
Spread to adjacent contacts	0.43	0.45	0.34	-0.45 to 1

A negative coefficient means the outcome variable decreases by that amount when the explanatory variable is adjusted for. FLE: frontal lobe epilepsy, TLE: temporal lobe epilepsy.

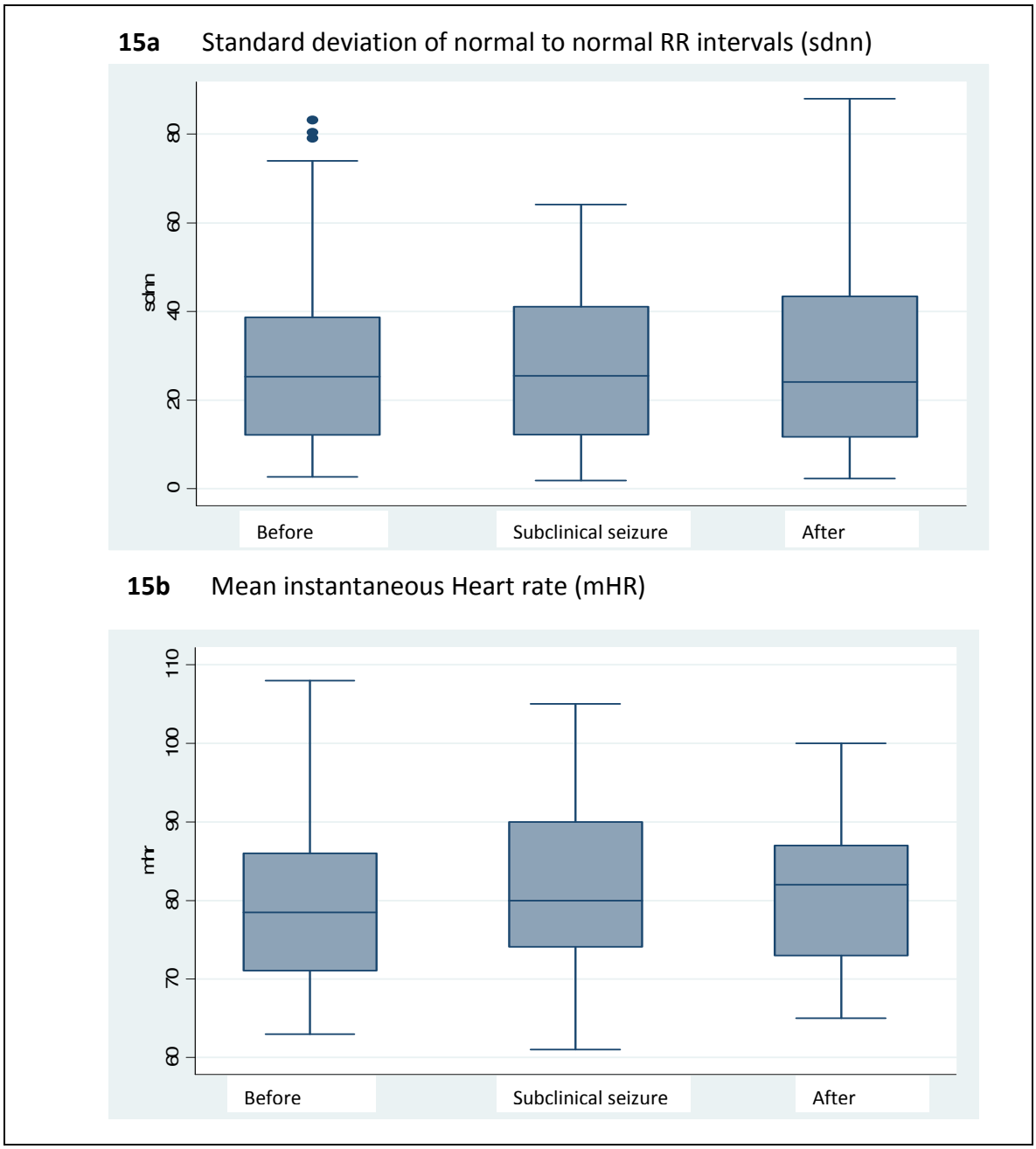


Figure 15 Box plots of the overall sdnn (a) and the mean instantaneous heart rate (b) in the three experimental time periods. No significant differences (pooled data) in HRV, whereas HR was slightly increased (p= 0.023) during the subclinical seizure. The values are presented as medians (horizontal bars) with the interquartile range at the end of the boxes. The vertical capped bars represent the maximum and minimum values above and below the interquartile ranges. The dots are the outliers.

4.5 Discussion

In summary, HRV does not change during subclinical seizures. Mean heart rate increases slightly during subclinical seizures. Patients with temporal lobe epilepsy have reduced HRV and increased mean heart rate. This is particularly so with left temporal lobe epilepsy. In this study, I have used data from short 10 seconds ECG recordings and observed, in contrast to a previous study which included mostly patients with scalp EEG recordings (Weil et al. 2005), only minor changes in HR independent of the duration of the subclinical pattern. This difference might be due to the limited extent of the electrographic pattern in these subclinical seizures in the study, and it may be the case that clear changes in mean heart rate occur only when there is more extensive spread of electrographic seizure activity (Epstein et al. 1992). Furthermore, HRV did not change during or after subclinical patterns; these findings are in accordance with those from recent studies that investigated HRV during epileptiform activity and subclinical generalised spike and wave activity in children (Assaf et al. 2008; Longin et al. 2007). I have also found that the influence of the frontal and temporal lobes on the mean heart rate and heart rate variability are different. Temporal lobe epileptogenicity, in particular, is associated with a low HRV and high mHR. These findings suggest that neuronal networks within temporal and frontal lobes have a differential impact on autonomic function. However, I cannot rule out the possibility that the observed differences in autonomic function in the frontal and temporal lobes are, to some extent, due to differences in lesion anatomy or cerebral volume that is covered with different electrode types (grid versus depth and subdural strip).

In addition, temporal lobe epilepsy can cause extensive cortical dysfunction. Insula underfunctioning releases the inhibition provided to the brainstem autonomic centres and result in increased sympathetic function (Oppenheimer 2006; Oppenheimer 2007), reflected as reduced HRV. The finding that cardiac sympathetic tone is increased in patients with left temporal lobe epilepsy is consistent with the presumed asymmetric representation of autonomic function (Oppenheimer et al. 1990; Oppenheimer et al. 1992; Swartz et al. 1994; Zamrini et al. 1990), i.e. that inactivation of right hemisphere leads to decrease in HR whereas left-sided inactivation to an increased HR. Likewise, PET imaging and neuropsychological studies indicated interictal dysfunction of the affected brain regions; a lesion in the left-sided temporal lobe structures may lead to impaired

parasympathetic activity and a right-sided lesion to an impaired sympathetic activity. The finding of autonomic dysfunction with impaired parasympathetic activity and predominant sympathetic activity in left temporal lobe epilepsy is also consistent with earlier reports on interictal autonomic dysfunction in chronic epilepsy (Diehl et al. 1997; Evrengul et al. 2005; Hilz et al. 2002).

Chapter 5

Heart rate variability during clinical seizures in partial epilepsy

Abnormal cortical activity during overt epileptic seizures ("clinical seizures") recruits regions of the central autonomic network. It has been proposed that seizures modify cardiovascular autonomic function by the involvement of these areas during seizure propagation. Several studies in epilepsy suggests that there is an interictal autonomic disturbance in patients with epilepsy (Adjei et al. 2009; Devinsky et al. 1994; Devinsky 2004; Hilz et al. 2002; Mukherjee et al. 2009) however only a few describe ictal or peri-ictal cardiac autonomic dysfunction using the HRV (Toth et al. 2010). Abnormal cardiac autonomic function is thought to be one possible mechanism of SUDEP and as SUDEP occurs mainly in the ictal or immediate peri-ictal period of a seizure (Langan et al. 2005; Nashef et al. 1997; Nieminen et al. 2010), one could hypothesise that this is also the time of maximal cardiac autonomic change. However, the extent and severity of autonomic dysfunction during this period is unknown. Several different patterns of autonomic dysfunction have been postulated to occur in the peri-ictal period, and common to all is the potential for the autonomic disturbance to result in peri-ictal arrhythmia, a known risk for sudden death and a potential mechanism for SUDEP (Nilsson et al. 1999; Rugg-Gunn et al. 2000; Surges et al. 2009c).

5.1 Aim

The aim in this study was to test the hypothesis that changes occur in the heart rate variability (as an index of autonomic function) during clinically overt complex partial seizures. Also, if these changes do occur, to determine whether they can be used to localise the seizure focus within the cerebral cortex.

5.2 Methodology

Only patients who had complex partial seizures during video telemetry were included in this study. SDNN and mean heart rate were done on 10 second periods of ECG which were free of artefacts. See chapter 3 section 3.3 for comprehensive description of methods.

5.3 Statistical Analysis

Ictal and postictal HRV were compared to the preictal HRV using linear mixed model analysis. See chapter 3 section 3.6.

5.4 Results

Summary of Clinical Characteristics

A total of 109 chronic epilepsy patients (56 males and 53 females) who were under evaluation for epilepsy surgery were included in this study. The mean duration of epilepsy was 21(12) years and about 47% of these patients were on carbamazepine in addition to other antiepileptic drugs. 70 patients had temporal lobe epilepsy and 39 had extra temporal lobe epilepsy. 217 seizures were studied, 105 and 112 seizures localized to the right and left hemisphere respectively. 88 seizures emanated from the extratemporal lobe focus and 129 from a temporal lobe focus. The most common pathological finding on MRI was hippocampal sclerosis and in 40 patients no cause for the epilepsy was known and there was no abnormality on MRI. All patients had up to 96 hours of video EEG telemetry and between 1- 3 successive seizures were recorded from each patient. The mean seizure duration was 76(55) seconds.

Table 5.1 Patients clinical characteristics (n=109)

Clinical features		Observation(n)
Epilepsy duration/years mean(SD) range		21(12); 2 to 58
Seizure duration/secs mean(SD) range		76(55); 12 to 283
Age of patients/years mean(SD) range		35(11); 18 to 65
Gender/n	Male	56
	Female	53
Carbamazepine related polytherapy/n	Yes	51
	No	58
Hemispheric location of Epileptic focus/n	Left	57
	Right	52
Lobar Location of Epileptic focus/n	TLE	70
	exTLE	39
Total number of seizures/n		217

n number; exTLE extratemporal lobe epilepsy; TLE temporal lobe epilepsy; SD standard deviation

Table 5.2 MRI findings for all patients (n=109)

MRI pathology	Number of Patients
Normal MRI	40
Hippocampal sclerosis	35
Malformations of cortical development	11
Dysembryoplastic Nerve Cell Tumor	5
Tumors (not DNET)	5
Vascular Malformations	7
Traumatic Lesions	3
Ischaemic Lesions	2
Neurocutaneous syndromes	1

Up to 36 % of the patients had normal pathology on MRI and had probably cryptogenic partial epilepsy.

Summary of HRV indices

Overall characteristics of the measured HRV indices are presented in the following tables (5.3 to 5.5). The time domain indices; sdnn and mean instantaneous heart rate were analyzed from 10 second ECG segments.

Table 5.3 Comparison of sdnn and mHR in the three time periods

	Variables	Time1 Preictal mean(SD) range	Time 2 Ictal mean(SD) range	Time 3 Posticta l mean(SD) range
Sdnn	overall	34.02(19.55)6.*08-96.35*	18.88(12.92)2.*58-113.64*	33.11(20.38)*2.86-98.73*
	between	(17.14)9.*41-96.35*	(13.22)5.*74-113.64*	(18.18)4.*00-86.15*
	within	(11.53)*3.67-70.25*	(6.81) *1.09-57.86*	(12.11)8.*73-74.34*
mHR	overall	74(13)*50-143*	112(30)*60-197*	89(22)*58-192*
	between	(12)*51-117*	(26)*71-187*	(19)*56-142*
	within	(6)*39-110*	(15)*56-161*	(14)30-*153*

Heart rate variability compared in the periods before during and after the seizures showing the overall, between and within patient variation. Within patient variation remains smaller than between patient variation. Overall there is a marked reduction in sdnn during the seizure (P=0.0001) which returns to around preictal levels in the period 20 seconds after the seizure offset. Mean instantaneous heart increases during the seizure (P=0.0001) but remains fairly high after the seizure (P=0.0001). Sdnn: standard deviation of the normal to normal RR intervals over 10 seconds, mHR: mean instantaneous heart rate.

Table 5.4 Comparison between left and right hemispheric sides in TLE in the peri-ictal period

	variables	Left hemisphere mean(SD) range	Right hemisphere mean(SD) range
sdnn/ms	overall	26.94(19.45)*2.58-113.64*	27.95(17.71)*4.07-98.73*
	between	(13.43)*10.49-67.20*	(11.28)*10.85-70.01*
	within	(15.46)*12.15-89.66*	(14.44)*11.83-82.77*
mHR/bpm	overall	95(27)*51-187*	88(23)*58-188*
	between	(15)*62-128*	(14)*66-121*
	within	(24)*46-184*	(18)*71-165*

Heart rate variability is compared in the left and right hemispheric region in patients with temporal lobe epilepsy. The difference in sdnn (P=0.62) and mHR (P=0.29) is not significant. TLE: temporal lobe epilepsy.

Table 5.5 Comparison between left and right hemispheric sides in exTLE in the peri-ictal period.

	variables	Left hemisphere mean(SD) range	Right hemisphere mean(SD) range
sdnn/ms	overall	28.93(20.14)2*.86-89.9*	32.12(19.64)*6.71-86.67*
	between	(11.34)*13.26-51.45*	(10.87)*18.90-55.92*
	within	(16.67)*5.92-86.18*	(16.81)*4.01-76.50*
mHR/bpm	overall	93(9)*50-197*	91(30)*52-187*
	between	(17)*61-128*	(16)*70-124*
	within	(27)*40-172*	(24)*40-171*

HRV of the left and right hemispheric sides in patients with extratemporal lobe epilepsy is compared. There is no clear difference between the two sides in both sdnn (P=0.62) and mHR (P=0.29). Sdnn: standard deviation of normal to normal RR intervals, mHR: mean instantaneous heart rate, and exTLE: extratemporal lobe epilepsy.

Sdnn during complex partial seizures

On average, HRV decreases during seizures by about 15ms (P<0.001, 95%CI 12.24ms to 18.04ms) after adjusting for the effects of gender, age, number of successive seizures, seizure duration, epilepsy duration, lobar and hemispheric location of the epileptic focus and that due to carbamazepine polytherapy. There is no statistical difference between the postictal and preictal HRV (P=0.54). Overall, for every additional seizure after a first seizure, HRV decreases by about 4.7ms (P=0.012, 95%CI= 1.03ms to 8.34ms). Age

(P=0.79), gender (P=0.95), duration of seizure (P=0.39) hemispheric or lobar location (P=0.62 and P=0.09 respectively), carbamazepine treatment (P=0.20) and the duration of epilepsy (P=0.70) have no effects on the HRV during seizures.

Table 5.6 Results of sdnn analysis during complex partial seizures

sdnn/ms	coefficient	standard error	P value	95% Confidence interval
Time period1(preictal vs. ictal	-15.14	1.48	<0.001	-18.04 to -12.24
Time period2(preictal vs. postictal)	-0.90	1.48	0.54	-3.80 to 1.99
Gender(female vs. males)	0.14	2.29	0.95	-4.34 to 4.63
seizures	-4.68	1.87	0.012	-8.34 to -1.03
seizure duration/secs	0.013	0.02	0.39	-0.02 to 0.04
epilepsy duration/years	-0.05	0.13	0.71	-0.29 to 0.20
Age/years	-0.04	0.15	0.78	-0.34 to 0.25
Lobar location(TLE vs. exTLE)	-4.05	2.41	0.09	-8.77 to 0.67
Hemispheric Location(Left vs. Right)	-1.19	2.40	0.62	-5.91 to 3.51
CBZ related treatment	-2.97	2.32	0.20	-7.52 to 1.59

Multiple regression analysis tables showing the explanatory variables included in the final mixed model analysis for the sdnn. Coefficients represent the mathematical weighting of the explanatory variables on the outcome variable. Negative coefficients represent a decreased effect. CBZ carbamazepine; TLE temporal lobe epilepsy; exTLE extratemporal lobe epilepsy

Mean heart rate during complex partial seizures

On average, mean heart rate increases during seizures by about 39bpm (P<0.001, 95%CI=35bpm to 42bpm) and in the postictal state, the mean heart rate is high when compared to the preictal state by about 15bpm (P<0.001, 95%CI=12bpm to 19bpm) after the effects of age, sex, seizure duration, epilepsy duration lobar and hemispheric location of epileptic focus and carbamazepine related polytherapy have been adjusted for. Overall female patients with epilepsy have higher mean heart rates of about 6bpm more than their male counterparts (P=0.041, 95%CI=0.24bpm to 13bpm). On average every 1 second increase in the seizure duration will increase the peri-ictal mean heart rate by 0.04 bpm (P=0.024, 95%CI=0.01bpm to 0.08bpm). Both epilepsy duration and the age of the patient have significant effects on the peri-ictal mean heart rate. Overall every one year increase in the age of patient, decreases the peri-ictal mean heart rate by 1bpm (P=0.001, 95%CI= 0.3bpm to 1bpm) and for every additional year of epilepsy, peri-ictal mean heart rate increases by 0.34bpm (P=0.035, 95%CI=0.02bpm to 0.7bpm) after adjusting for the effects of all the other variables. Finally, hemispheric location (P=0.29),

lobar location (P=0.79), number of successive seizures (P=0.78) and carbamazepine related polytherapy (P=0.22) do not influence the mean heart rate.

Table 5.7 Results of mHR analysis during clinical seizures

mHR/bpm	coefficient	standard error	P value	95% Confidence interval
Time period1(preictal vs. ictal	39	2	<0.001	35 to 42
Time period2(preictal vs. postictal)	16	2	<0.001	12 to 19
Gender(female vs. males)	6	3	0.041	0.24 to 13
seizures	-1	2	0.78	-5 to 3
seizure duration/secs	0.04	0.02	0.024	0.01 to 0.08
epilepsy duration/years	0.34	0.2	0.035	0.02 to 0.7
Age/years	-1	0.2	0.001	-1 to -0.3
Lobar location(TLE vs. exTLE)	-1	3	0.79	-7 to 5
Hemispheric Location(Left vs. Right)	3	3	0.29	-3 to 9
CBZ related treatment	4	3	0.22	-2 to 9

Multiple regression analysis tables showing the explanatory variables included in the final mixed model analysis for the mHR. Coefficients represent the mathematical weighting of the explanatory variables on the outcome variable. Negative coefficients represent a decreased effect whereas a positive coefficient refers to increased effect of the explanatory variable on the outcome variable. CBZ carbamazepine; TLE temporal lobe epilepsy; exTLE extratemporal lobe epilepsy; mHR mean instantaneous heart rate

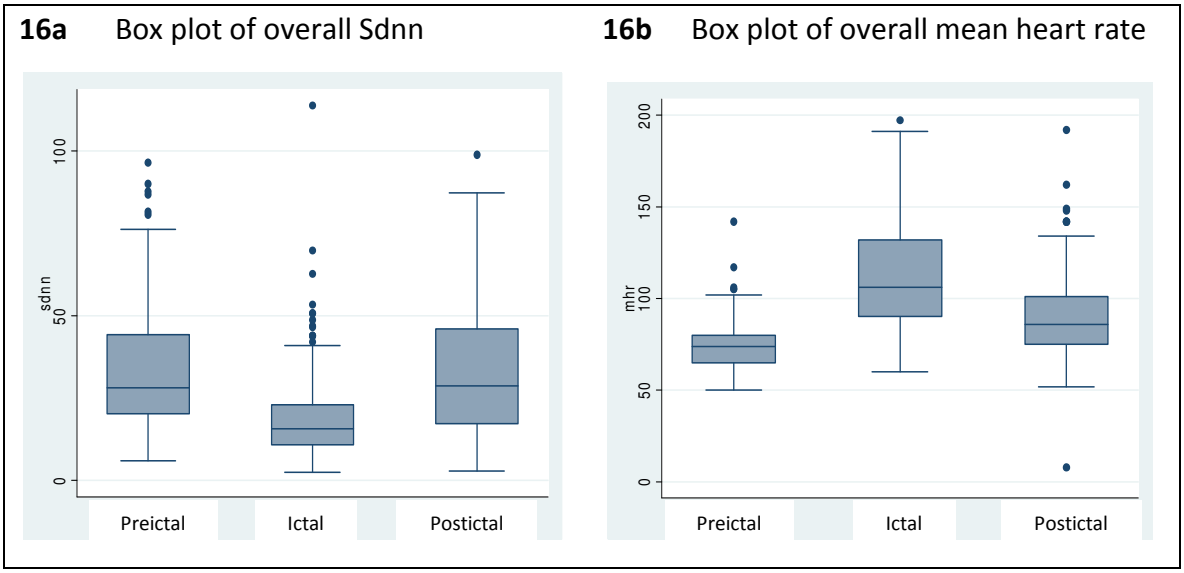


Figure 16 Box graphs of the sdnn and mHR. Values are presented as medians (horizontal bars) with the interquartile range at the end of boxes. The vertical capped bars represent the maximum and minimum values above the upper and lower quartiles respectively. The dots represent the outliers. On the average, sdnn decreases (P<0.001) during the ictal phase and returns to preictal levels at the end of the seizure (P=0.54). However the mean heart rate increases during the ictal phase (P<0.001) and decreases after the seizure but remains significantly higher than the preictal level (P<0.001).

5.5 Discussion

In summary, I have found that HRV decreases during clinical seizures and decreases with every additional seizure after a first seizure. The mean heart rate increases during seizures. The age of patient and duration of epilepsy decreases and increases the peri-ictal mean heart rate respectively. Neither the hemispheric location nor lobar location of the epileptic focus has any significant effect on the changes of the heart rate variability during seizures. In this study, I have evaluated heart rate variability in the immediate preictal phase (20 seconds before seizure onset), mid ictal phase and the immediate postictal (20 seconds after the seizure offset in complex partial seizures from patients with chronic medically refractory epilepsy. In addition, I have demonstrated that the HRV is reduced whereas the mean heart rate is increased during epileptic seizures. I have also found HRV to decrease with successive seizures not particularly seizure clusters. About half of the patients in this group were on carbamazepine and since all the patients had drug reduction during telemetry, this may be related to the enhancement of cardiac sympathetic tone following sudden withdrawal of carbamazepine (Hennessy et al. 2001). Ictal tachycardia was observed to be the most common cardiac rhythm change during epileptic seizures, as has been reported before (Jansen et al. 2010; Leutmezer et al. 2003; O'Regan et al. 2005).

The findings suggest that an epileptic seizure irrespective of the localization of the epileptic focus causes reversible increase in cardiac sympathetic activity which may be further compromised when seizures are repetitive. This is the first study to have looked at the ictal autonomic changes of HRV. An earlier study evaluated peri-ictal rather than the ictal HRV and the results suggested postictal decrease of HRV which persisted for as long as 6 hours after seizure offset (Darbin et al. 2002; Mayer et al. 2004; Naritoku et al. 2003; Toth et al. 2010) and my findings provide confirmation of this and show that the change in HRV is triggered during the ictus itself. One possible significance of these findings is that the timing of the reduction in HRV during the seizure, starting ictally and extending into the immediate postictal period, is similar to that of the occurrence of SUDEP. During epileptic seizures, the reduced HRV is due to an ictally-induced increase in sympathetic tone. Similar findings of increased sympathetic tone during seizures have been found in animal models of epilepsy (Lathers et al. 1982; Sakamoto et al. 2008). The

marked reduction in the HRV during the seizure and the persisting reduction in successive seizures are interesting. There are many studies that have linked epileptic seizures with abnormal function in the autonomic nervous system (Baumgartner et al. 2001; Sakamoto et al. 2008; Surges et al. 2010a; Toth et al. 2010), but none have previously been able to determine that this is direct consequence of ictal activity. Propagation of the electrical component of seizures in the cortex is associated with the recruitment of contiguous areas in the cortex - central autonomic network and disinhibition of the cardiovascular control centers in the lower brainstem. The increase in the sympathetic tone may result in tachyarrhythmia typically ventricular and atrial fibrillation (Oppenheimer 1993; Oppenheimer 2007; Zhang et al. 2000b) and several clinical studies have described tachyarrhythmia, bradyarrythmias and asystole during epileptic seizures (Opherk et al. 2002a; Rugg-Gunn et al. 2000; Standridge et al. 2010; Zijlmans et al. 2002). This is clearly a potential mechanism for SUDEP (Nilsson et al. 1999; Sakamoto et al. 2008). The findings from all these studies and from my study can be taken to imply that during an epileptic seizure a major increase in cardiovascular sympathetic tone (decreased HRV) occurs which may overwhelm the autonomic reflex mechanisms.

Hemispheric and lobar location of the epileptic focus did not influence the HRV in contrast to the findings of an earlier study (Toth et al. 2010). In that study the timing for HRV sampling at 20 min postictal made it more interictal than peri-ictal and the former has been found to be associated with asymmetry of autonomic function. Increased cerebral metabolism occurs in the epileptogenic zones, as can be demonstrated for instance by ictal SPECT (Adjei et al. 2009; Kazemi et al. 2010; Lamusuo et al. 1997; Wong et al. 2010). Also there is evidence for interhemispheric spread of electrical activity during complex partial seizures (Eross et al. 2009; Seyal et al. 2009). These and the findings in this study show that there is disruption of the interictal hemispheric localization of autonomic function in the cerebral cortex during the ictal period. The effects of age and epilepsy duration on the mean heart rate, mirrors the global changes to mean heart rate with these parameters (Devinsky et al. 1994; Earnest et al. 1992; Opeskin et al. 2000) and the fact that the peri-ictal HRV is not affected by these factors may be because of the lack of correlation between the HRV and heart rate (Sztajzel et al. 2008).

Chapter 6

Interictal and circadian rythm of heart rate variability in partial epilepsy

The autonomic tone in the cardiovascular system is maintained under a distinct circadian rhythm by the hypothalamo-pituitary pineal network and the adrenergic system (Singh et al. 2003). It has been established in previous studies that the heart rate variability (HRV) is higher during the night time than during the day time. However, a detailed analysis and the significance of this phenomenon are still under investigation (Bonnemeier et al. 2003; Carrington et al. 2003; Malpas et al. 1990). It has been shown that when there is vagal nerve dysfunction, the diurnal pattern of the HRV is unaltered (Malpas et al. 1990). Thus, the increase in HRV at night observed in normal individuals is not related to increased vagal activity but to a withdrawal or reduced cardiac sympathetic tone during the night. Using conventional heart rate variability measures several investigators have been able to confirm that there is reduced sympathetic modulation during the night in healthy individuals (Furlan et al. 1990; Sapoznikov et al. 1992; Yamasaki et al. 1996). This normal diurnal fluctuation of the HRV is disrupted in patients with myocardial infarction, angina pectoris, diabetes mellitus and epilepsy (Chokroverty 2008; Ewing et al. 1991; Ronkainen et al. 2005; Tomson et al. 1998; Tomson et al. 2008). Bearing in mind that there is a diurnal pattern in the onset for both ischemic cardiac events and sudden cardiac death in the general population (Bonnemeier et al. 2003; Korpelainen et al. 1997), and the fact that abnormal diurnal HRV dynamics has been previously suggested in epilepsy (Ronkainen et al. 2005), it is possible that epilepsy may disrupt the heart rate variability and its circadian rhythm.

6.1 Aim

This study was done to evaluate heart rate variability, in normal day and night cycles in patients with epilepsy in order to test the hypothesis that intractable epilepsy can disrupt the heart rate variability and its circadian rhythm.

6.2 Methodology

HRV indices were done on 5 minute sections of ECG taken at the beginning of each hour in the interictal period in patients with chronic medically intractable epilepsy. Details in chapter 3, section 3.3.

6.3 Statistical Analysis

Generalised estimation equations were used to evaluate the effect of patient factors on the HRV indices. See chapter 3 section 3.6 for details.

6.4 Results

Summary of clinical characteristics

A total of 66 patients with chronic epilepsy, 34 males and 32 females, were included in this study. 40 patients had temporal lobe epilepsy, 20 lateralised to the left hemisphere and 20 lateralised to the right hemisphere. Of the 26 with extratemporal lobe epilepsy, the focus was in the left hemisphere in 12 and in the right hemisphere in 14. One subject had both an hypothalamic hamartoma and right frontal lobe cortical dysplasia. However, the epileptogenic zone was found to be in the right frontal lobe, there was no record of gelastic seizures and therefore this subject was included in the frontal lobe epilepsy group. All patients were on more than one antiepileptic drug with up to 45% patients receiving carbamazepine as part of polytherapy at the time of inclusion in this study. Drug reduction was carried out in all 66 patients. A few patients were sleep deprived. However, heart rate variability data was sampled at the onset of recording in the first 24 hours before sleep deprivation and drug withdrawal had taken place.

Table 6.1 Summary of clinical characteristics of the group (n=66)

Clinical Characteristic	Observation
Epilepsy duration mean (SD) (range)years	22(11)(5-59)
Age mean(SD) (range) years	36(9)(19-61)
Epilepsy Type	40 TLE
	25 FLE
	1 PLE
Gender	34 males
	32 females
Yearly Seizure Frequency median (interquartile range)	72(28 to 156)
Carbamazepine polytherapy	30

TLE: Temporal lobe epilepsy, FLE: Frontal lobe epilepsy, PLE: Parietal lobe epilepsy.

Summary of HRV

Data has been summarised showing the overall, between and within individual variation. These are presented in tables 5.2-5.4. Figure 17 summarises the overall Night vs. Day differences for all the measured HRV indices.

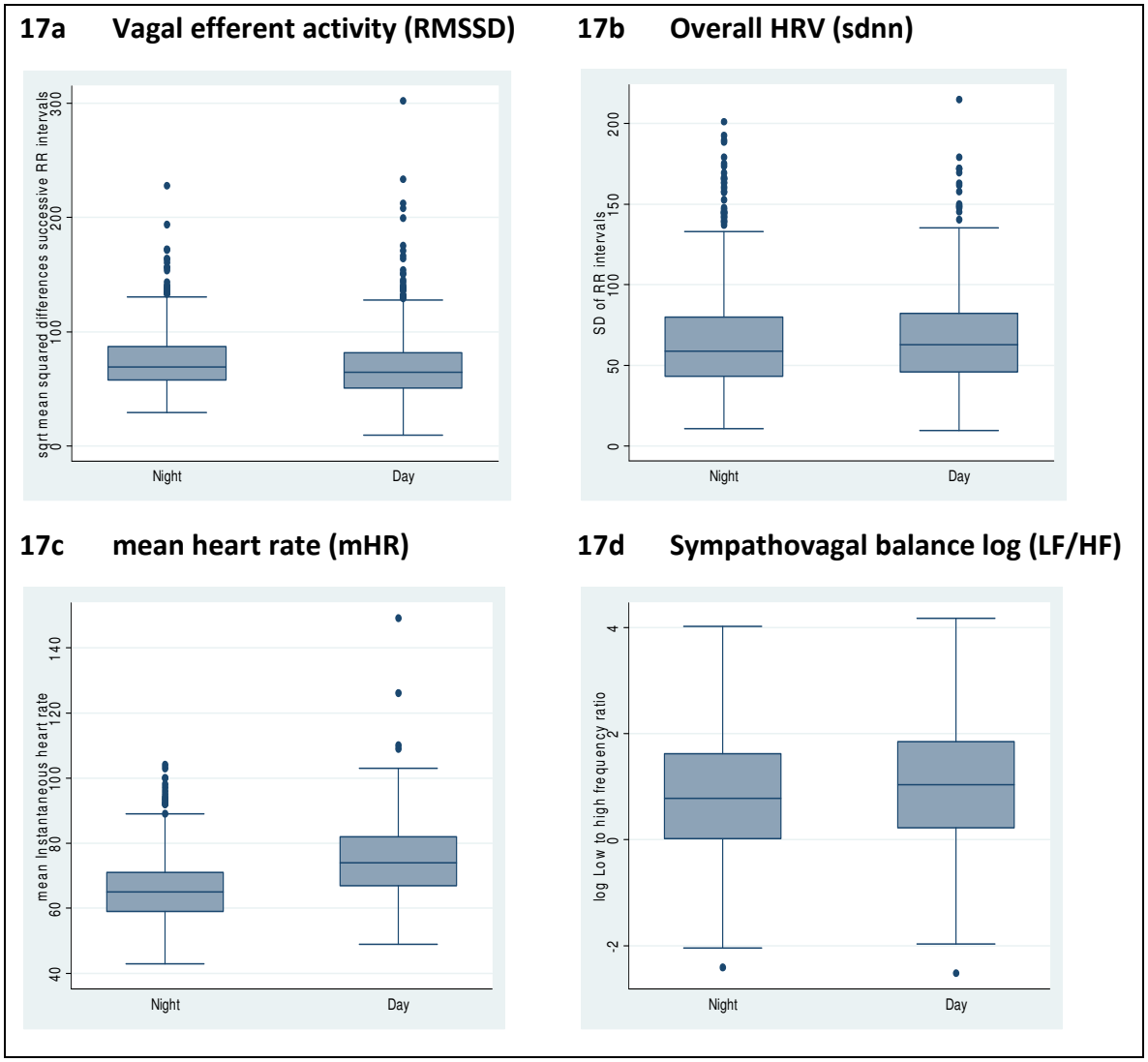


Figure 17 The Box graphs show summary of night (left hand side) and day (right hand side) of all the measured HRV indices in all patients with epilepsy (n=66). Values are presented as medians (horizontal bars) with the interquartile range at the end of boxes. The vertical capped bars represent the maximum and minimum values above the upper and lower quartiles respectively. The dots represent the outliers. Note LF/HF has been analysed as the log transformation because of skewness of data (positively skewed). Day values are significantly different from corresponding night values except for the sdnn heart rate variability. RMSSD (P=0.02), sdnn (P=0.94) mHR (P=0.0001) and Log (LF/HF) (P=0.002). RMSSD Square root of mean squared RR interval differences; sdnn Standard deviation of RR intervals in a given segment of ECG; mHR Mean instantaneous heart rate; Log(LF/HF) Logarithmic transformation of Low to High frequency ratio.

Table 6.2 Comparison of Day and Night HRV in all patients

Variable		Day			Night		
		Mean	**SD**	**Range**	**Mean**	**SD**	**Range**
RMSSD/ms	Overall	70.02	27.50	9.95 to 301.83	74.45	23.73	29.54 to 227.74
	Between		18.13	40.51 to 142.64		17.02	49.68 to 137.61
	Within		20.78	7.76 to 229.22		16.65	24.70 to 164.57
Sdnn/ms	Overall	65.96	28.50	9.61 to 214.80	65.53	31.94	10.72 to 200.96
	Between		19.04	30.23 to 123.29		18.85	33.97 to 121.69
	Within		21.32	0.17 to 159.89		25.89	9.35 to 171.39
mHR/bpm	Overall	74	11	49 to 149	66	10	43 to 104
	Between		8	57 to 90		7	50 to 87
	Within		7	54 to 139		7	49 to 99
Log(LF/HF)	Overall	1.04	1.12	-2.53 to 4.17	0.81	1.15	-2.41 to 4.02
	Between		0.69	-0.33 to 2.68		0.70	-0.42 to 2.78
	Within		0.89	-1.53 to 4.19		0.92	-1.84 to 3.73

There is higher within individual variation as compared to between individual variations. Night time values for heart rate variability differ from the day time. Sdnn Standard deviation of RR intervals; RMSSD square root of the mean squared RR interval differences; mHR mean instantaneous heart rate, SD standard deviation.

Table 6.3 Comparison of HRV in extratemporal lobe epilepsy patients

Variable		Left hemisphere			Right hemisphere		
		Mean	**SD**	**Range**	**Mean**	**SD**	**Range**
RMSSD/ms	Overall	69.64	20.42	29.54 to 145.45	86.71	34.83	30.27 to 301.83
	Between		11.02	50.87 to 85.01		24.46	50.34 to 130.58
	Within		17.51	27.98 to 134.67		25.67	28.97 to 257.96
Sdnn/ms	Overall	64.21	28.62	16.22 to 192.5	78.04	33.49	10.82 to 214.8
	Between		12.97	40.95 to 78.23		22.52	46.79 to 120.45
	Within		25.82	18.63 to 184.21		25.53	15.25 to 172. 40
mHR/bpm	Overall	70	11	46 to 103	64	12	43 to 109
	Between		7	59 to 80		9	55 to 87
	Within		9	47 to 93		7	53 to 92
Log(LF/HF)	Overall	0.91	1.08	-2.52 to 4.03	0.60	1.01	-2.04 to 3.87
	Between		0.64	-2.50 to 1.92		0.51	-0.10 to 1.58
	Within		0.90	-2.03 to 3.15		0.88	-1.71 to 3.13

In the extratemporal lobe epilepsy group, heart rate variability indices recorded from the right hemisphere are indicative of an enhanced parasympathetic tone. Sdnn Standard deviation of RR intervals; rMSSD square root of the mean squared RR interval differences; mHR mean instantaneous heart rate, SD standard deviation.

Table 6.4 Comparison of HRV in Temporal lobe epilepsy patients

Variable		Left hemisphere			Right hemisphere		
		Mean	**SD**	**Range**	**Mean**	**SD**	**Range**
RMSSD/ms	Overall	67.89	22.30	9.95 to 212.34	68.94	21.52	29.82 to 233.24
	Between		11.91	46.02 to 90.47		12.71	51.48 to 102.37
	Within		19.37	4.85 to 220.22		17.59	34.01 to 213 .8
Sdnn/ms	Overall	61.85	30.01	10.72 to 188.55	62.77	27.14	9.61 to 160.59
	Between		16.65	35.30 to 96.89		13.81	37.33 to 87.81
	Within		25.13	3.79 to 171.00		23.56	8.85 to 150.14
mHR/bpm	Overall	70	11	46 to 149	70	10	46 to 110
	Between		7	56 to 84		7	58 to 81
	Within		9	50 to 144		8	52 to 101
Log(LF/HF)	Overall	1.16	1.17	1.96 to 4.17	0.89	1.18	-2.04 to 4.12
	Between		0.70	0.06 to 2.45		0.79	-0.13 to 2.54
	Within		0.97	1.54 to 4.17			-1.58 to 3.74

In the temporal lobe epilepsy patients excepting the (LF/HF), which shows a left to right sympathetic predominance, there are no obvious left to right difference in the other indices. Sdnn Standard deviation of RR intervals; RMSSD square root of the mean squared RR interval differences; mHR mean instantaneous heart rate, SD standard deviation.

Diurnal Patterns of HRV indices

The diurnal patterns of the measured HRV indices are similar to that described in normal healthy adults (Bonnemeier et al. 2003).

The sympathovagal balance curve for all patients (figure 18a) shows the sympathovagal index to gradually increase from midnight through the night, staying high throughout the day with a peak at around midday. This is followed by a gradual decrease reaching lowest level at around midnight.

Instantaneous heart rates curve for all patients (figure 18b) shows the mean heart rate to gradually decline from midnight. It is at a nadir between 4 and 6 am (just before waking up), peaks at between 8-9 am and then decreases gradually, remaining fairly constant during the day. At 6pm it begins to fall again to the low night time levels.

Overall heart rate variability curve for all patients (figure 18c), begins to increase from the midnight and shows a peak at around 7am (waking up). This is followed by the drop between 8-9 am and a sustained decrease throughout the day decreasing to low levels around midnight, and then the cycle begins again.

Vagal efferent activity curve (figure 18d), shows a night time high compared to the day time. It is highest between 4-6 am (just before waking) and then begins to fall after wake up, but remains fairly constant at a relative low throughout the day and rises again by midnight.

Figure 18a

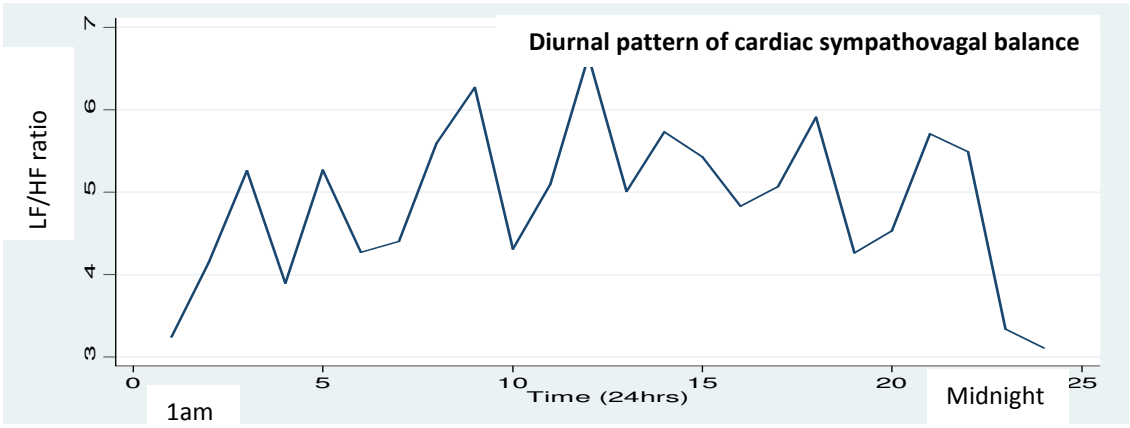


Figure 18b

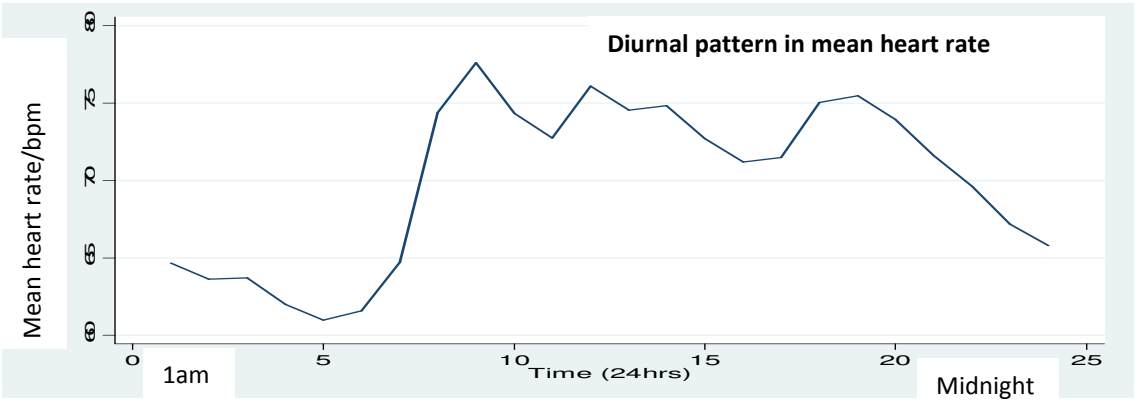


Figure 18c

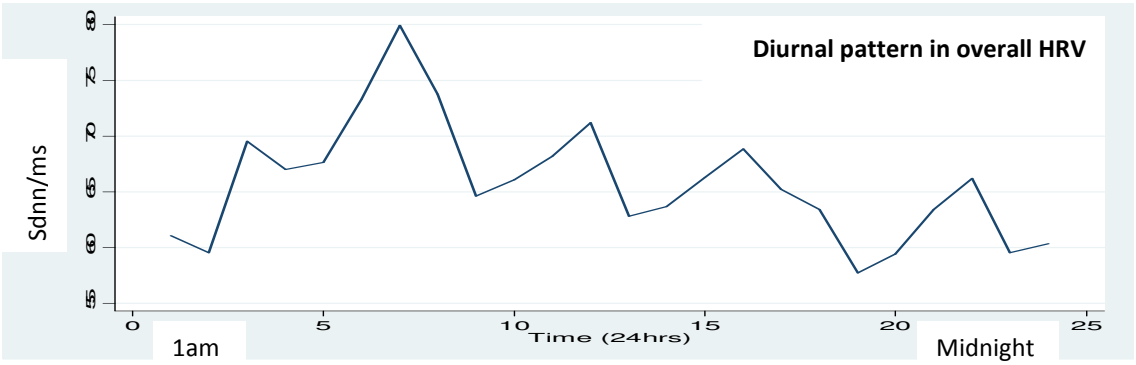


Figure 18d

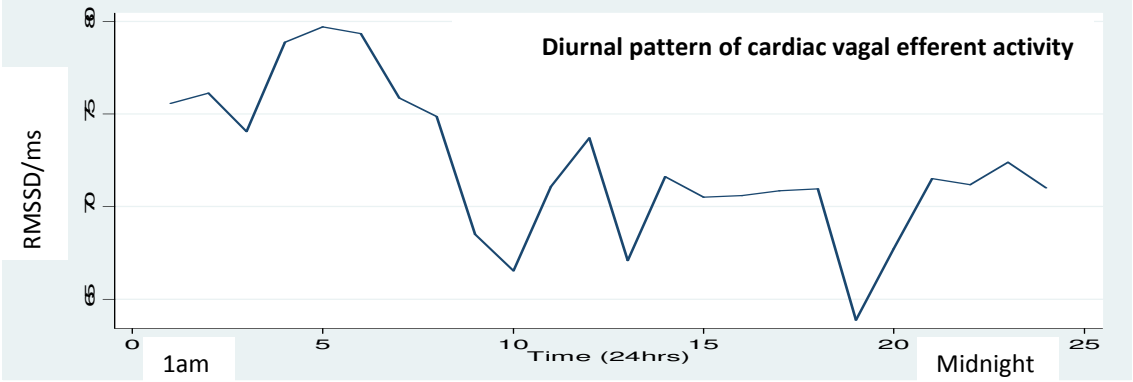


Figure 18 Overall, measured HRV indices show a diurnal trend.

Diurnal and interictal Cardiac Vagal activity (RMSSD)

RMSSD is an HRV measure that determines cardiac vagal activity. On average, the day time HRV are 4.15ms (P=0.02, 95% CI= 0.79ms to 7.52ms) lower than the night time when the effects of age, gender, yearly seizure frequency, duration of epilepsy, lobar location and the hemispheric laterality of epileptic focus are adjusted for. On average, the HRV goes down by 0.43ms (P<0.001, 95% CI= 0.20ms to 0.65ms,) for every one year increase in the duration of uncontrolled epilepsy. There is no statistical significant difference between patients with temporal and extratemporal lobe epilepsy (P=0.91) and also within the left and right hemispheric side for patients with temporal lobe epilepsy (P=0.93). However within patients with extratemporal lobe epilepsy, HRV was higher on the right hemispheric side than on the left by about 19 ms (P<0.001, 95% CI=12.06ms to 25.22ms).

Table 6.5 Effects of the Day vs. Night and other epilepsy factors on RMSSD

RMSSD/ms	Coefficient	Standard Error	P value	95% Confidence Interval
Day vs. Night	-4.15	1.71	0.02	-7.52 to – 0.79
Gender(Females vs. males)	0.31	2.01	0.87	-3.62 to 4.28
Age	0.09	0.15	0.55	-0.19 to 0.37
CBZ tx vs. Non CBZ tx	-0.49	2.11	0.82	-4.62 to 3.63
Yearly seizure frequency	0.002	0.004	0.53	-0.0052 to 0.01
epilepsy duration	-0.43	0.11	<0.001	-0.65 to -0.20
Location(TLE vs. exTLE)	-0.35	2.99	0.91	-6.21 to 5.51
exTLE(Right vs. Left)	18.64	3.36	<0.001	12.06 to 25.22
TLE(Right vs. Left)	0.22	2.43	0.93	-4.55 to 4.99

RMSSD Square root of the mean squared differences of successive RR intervals is a measure of vagal efferent activity. Negative coefficients signify a decrease of the RMSSD (response variable) by that figure for any change in the determined variables (explanatory variable). Thus, RMSSD decreases by 0.43ms for every additional year of uncontrolled epilepsy (P<0.001, 95%CI 0.20 to 0.65). In patients with extratemporal lobe epilepsy (right compared to left hemispheric localisation of epileptic focus), RMSSD is higher by about 19ms (P<0.001, 95%CI 12.06 to 25.22). Extra temporal lobe epilepsy here refers to frontal lobe epilepsy. TLE, temporal lobe epilepsy, exTLE, extratemporal lobe epilepsy, CBZ tx, polytherapy with carbamazepine, Left, left hemispheric side and Right, right hemispheric side.

Diurnal and interictal mean heart rate (mHR)

On average, the day time mean heart rates are higher than the night by about 6bpm (P<0.001, 95% CI=4bpm to7bpm). On average for every additional year a patient has uncontrolled epilepsy, mean heart rate goes up by 0.3 bpm (P<0.001, 95% CI=0.2bpm to 0.5bpm). Overall, the mean heart rate decreases by 0.3bpm for every year increase in the patients age (P<0.001, 95% CI=0.2bpm to 0.5bpm). When the interaction between the age and duration epilepsy was evaluated, it was found that the overall effect of the two is to increase the mean heart rate by 0.002bpm for every additional increase in patient age and epilepsy duration (P=0.006, 95% CI 0.0007 to 0.004). In female patients, the mean heart rate increases by about 5 bpm (P<0.001, 95% CI=3bpm to 7bpm). On average, patients with temporal lobe epilepsy have lower mean heart rate of about 3 bpm (P=0.046, 95% CI= 0.1bpm to 6bpm,). There is no statistical difference between the left and right hemispheric side in patients with both temporal and extratemporal lobe epilepsy (P=0.21 and 0.063 respectively).

Table 6.6 Effects of the Day vs. Night and other epilepsy factors on mHR

mean heart rate/bpm	Coefficient	Standard Error	P value	95% Confidence Interval
Day vs. Night	5.47	0.74	<0.001	4.02 to 6.92
Gender(Females vs. Males)	5.22	1.04	<0.001	3.18 to 7.27
Age	-0.33	0.08	<0.001	-0.48 to -0.18
CBZ tx vs. Non CBZ tx	-1.64	1.09	0.13	-3.78 to 0.49
Yearly seizure frequency	0.001	0.002	0.54	-0.003 to 0.005
epilepsy duration	0.33	0.06	<0.001	0.22 to 0.45
Location (TLE vs. exTLE)	-3.00	1.51	0.046	-5.95 to -0.05
exTLE(Right vs. Left)	-3.20	1.72	0.063	-6.58 to 0.17
TLE(Right vs. Left)	1.56	1.25	0.21	-0.90 to 4.03

CBZ tx, polytherapy with carbamazepine, exTLE, extra temporal lobe epilepsy, TLE Temporal lobe epilepsy. Negative coefficients imply the explanatory variables decreases the response variable. The resultant interaction between the patient age and epilepsy duration is an increase of the mean heart rate by about 0.002bpm (P=0.006, 95% CI 0.0007bpm to 0.005bpm) for every additional year.

Diurnal and interictal sdnn

On average, the difference between day and night time sdnn heart rate variability is not significant (P=0.94). The effects of gender (P=0.70), age (P=0.22), treatment with carbamazepine (P=0.74), yearly seizure frequency (P=0.43) and of location in either temporal or extratemporal lobe (P=0.98) on the sdnn were not significant. However, within the patients with extratemporal lobe epilepsy, sdnn is higher on the right hemispheric side compared to the left hemispheric side by 16.9ms (P<0.001, 95% CI= 9.61ms to 24.19ms). Finally, on the average, for every additional year the patient has epilepsy and after adjusting for the effects of the other variables, sdnn heart rate variability decreases by 0.49ms (P<0.001, 95% CI= 0.25ms to 0.74ms).

Table 6.7 Effects of Day vs. Night and other epilepsy variables on sdnn

SDNN/ms	Coefficient	Standard Error	P value	95% Confidence Interval
Day vs. Night	-0.15	1.95	0.94	-3.98 to 3.67
Gender(Female vs. Male)	0.84	2.23	0.70	-3.52 to 5.22
Age	-0.19	0.16	0.22	-0.5 to 0.11
CBZ tx vs. Non CBZ tx	0.75	2.32	0.74	-3.81 to 5.31
Yearly seizure frequency	-0.003	0.004	0.43	-0.012 to 0.005
epilepsy duration	-0.49	0.12	<0.001	-0.74 to -0.25
Location (TLE vs. exTLE)	0.07	3.32	0.98	-6.42 to 6.58
exTLE(Right vs. Left)	16.90	3.71	<0.001	9.61 to 24.19
TLE(Right vs. Left)	0.53	2.69	0.84	-4.74 to 5.82

SDNN, Standard deviation of normal to normal RR intervals, CBZ tx, polytherapy with carbamazepine, exTLE, extra temporal lobe epilepsy, TLE Temporal lobe epilepsy. Negative coefficients imply the explanatory variables decreases the response variable. Therefore, the SDNN decreases by 0.49ms for every additional year of epilepsy (P<0.001, 95%CI 0.25 to 0.75). In addition the right hemisphere localisation of the epileptogenic region is associated with increased SDNN (P<0.001, 95%CI 9.61 to 24.19).

Diurnal and interictal Cardiac sympathovagal balance (LF/HF)

On average, day time cardiac sympathovagal balance (LF/HF) is higher than the night time by about 0.21points (P=0.002, 95% CI 0.08 to 0.35). On average, in female patients with epilepsy sympathovagal balance is lower by about 0.51points (P<0.001, 95% CI 0.36 to 0.66). On average, every additional year increase in the epilepsy duration, cardiac sympathovagal balance increases by 0.01 points (P<0.001, 95% CI 0.001 to 0.018). Antiepileptic drug polytherapy with carbamazepine increases cardiac sympathovagal balance by 0.15 points (P=0.05, 95% CI 0.001 to 0.31). Overall for every additional year in age of patient, sympathovagal balance increases by 0.02 points (P=0.023, 95% CI 0.01 to 0.03). Sympathovagal balance is high in patients with temporal lobe epilepsy by 0.53 points (P<0.001, 95% CI 0.31 to 0.76). However, within the patients with temporal lobe epilepsy, right hemisphere location decreases the sympathovagal balance by 0.28 points (P=0.003, 95% CI 0.10 to 0.46). On average, a one point increase in the yearly seizure frequency will increase the sympathovagal balance by 0.0004 points (P<0.001, 95% CI 0.0002 to 0.0008).

Table 6.8 Effects of Day vs. Night and other epilepsy factors on LF/HF

Log(LF/HF)	Coefficient	Standard Error	P value	95% Confidence Interval
Day vs. Night	0.21	0.07	0.002	0.08 to 0.35
Gender(Female vs. Male)	-0.51	0.08	<0.001	-0.66 to -0.36
Age of Patient	0.02	0.006	<0.001	0.01 to 0.03
CBZ tx vs. Non CBZ tx	0.15	0.08	0.05	0.001 to 0.31
Yearly seizure frequency	0.0004	0.0001	0.001	0.0002 to 0.0008
epilepsy duration	0.01	0.004	0.023	0.001 to 0.018
Location (TLE vs. exTLE)	0.53	0.114	<0.001	0.31 to 0.76
ExTLE (Right vs. Left)	0.01	0.13	0.934	-0.24 to 0.26
TLE (Right vs. Left)	-0.28	0.09	0.003	-0.46 to -0.10

CBZ tx, polytherapy with carbamazepine, exTLE, extra temporal lobe epilepsy, TLE Temporal lobe epilepsy. Negative coefficients imply the explanatory variables decreases the response variable. Epilepsy duration increases the LF/HF ratio (P=0.23, 95%CI 0.001 to 0.18).

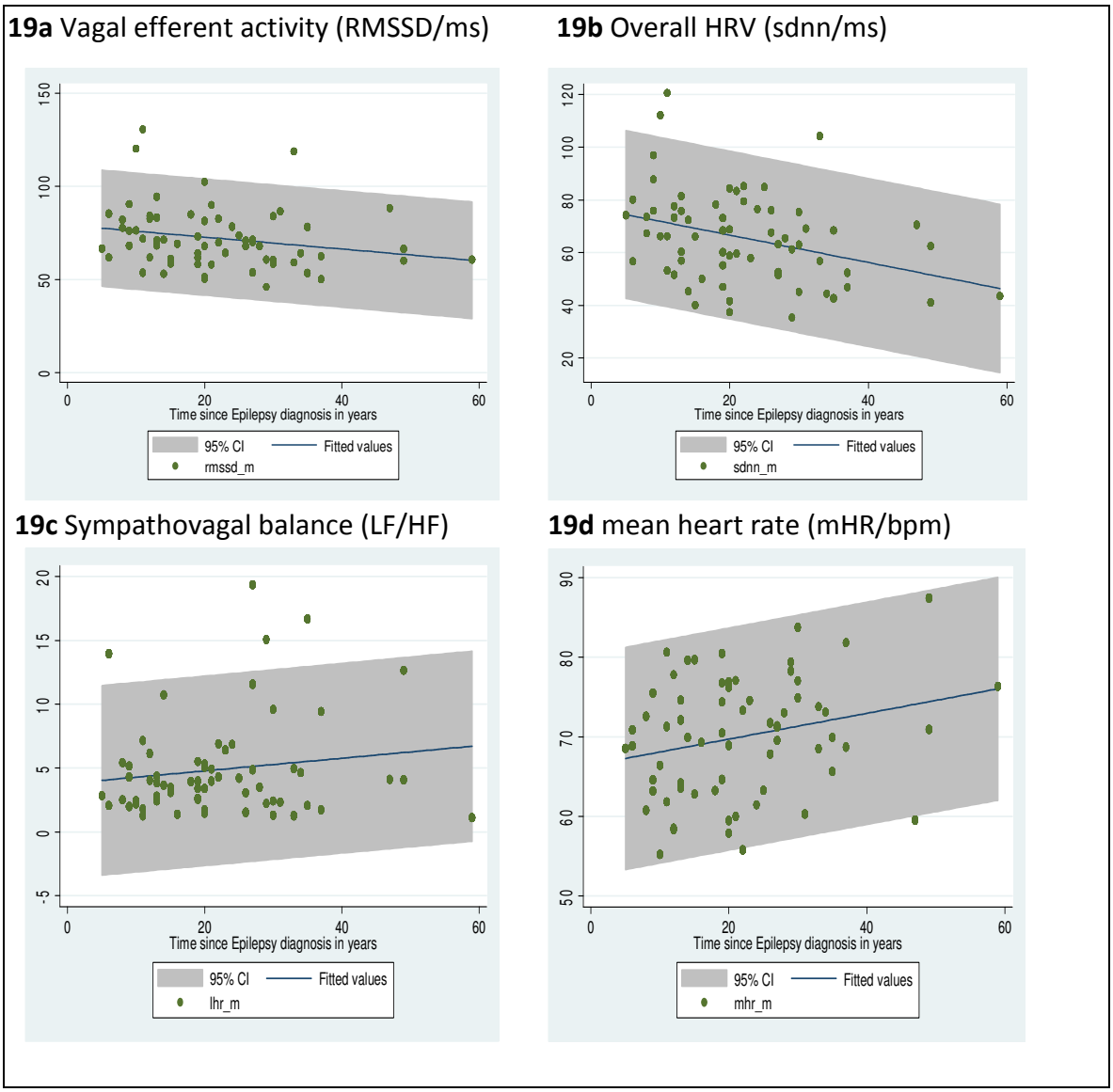


Figure 19 Scatter plots, the corresponding regression line and its 95% confidence interval or prediction bands of all the heart rate variability variables and epilepsy duration. These plots show the epilepsy duration increases mean heart rate and sympathovagal balance but reduces the vagal efferent activity and the overall heart rate variability. This means a prolonged medical history of epilepsy could increase cardiac sympathetic tone. However the prediction lines do not fit the data well, therefore other factors including the prolonged medical history of epilepsy affects cardiac sympathetic tone in epilepsy patients.

6.5 Discussion

In summary, the diurnal pattern of the HRV is preserved in patients with epilepsy. However, every additional yearly increase in epilepsy duration increase the cardiac sympathetic tone in patients with epilepsy. Even though the mean heart rate decreases with age, the combined effect of age and prolonged medical history of epilepsy is to increase the mean heart rate over time. Higher mean heart rates are seen in female epileptic patients. Carbamazepine polytherapy, high yearly seizure frequency and temporal lobe epilepsy increase cardiac sympathetic tone. Left and right hemisphere epileptogenicity control sympathetic and parasympathetic cardiac function respectively. The reduced cardiac vagal activity increased mean heart rate and an elevated cardiac sympathetic tone with the duration of active epilepsy means that epilepsy may depress heart rate variability. Antiepileptic drug use and seizure frequency were also found to reduce HRV independently of the effects of duration of epilepsy. A prolonged medical history of uncontrolled epilepsy is a risk factor for SUDEP (Devinsky et al. 1994; Earnest et al. 1992; Opeskin et al. 2000) and the finding in this study provide a potential pathophysiological explanation for this and a mechanism for cardiac arrhythmogenesis in chronic epilepsy patients.

But ageing in healthy individuals also results in decreased HRV and reduced cardiac vagal tone (Bonnemeier et al. 2003; Freeman et al. 2008; Hunt et al. 2001) and because the results have not been compared to non epileptic controls, the extent to which these HRV changes can be attributed to prolonged medical history of epilepsy cannot be readily ascertained. However, the statistical model adjusted for the effects of age in the study group and found it to be independent of the effects of duration of epilepsy. Therefore, it is possible to speculate that the findings of reduced HRV could be related to epilepsy as seen in this study. Reduced heart rate variability is a reliable predictor of death due to arrhythmias in other patient groups because of increased cardiac sympathetic tone (Jons et al. 2010; Smilde et al. 2009), and by extension, it is thus plausible that the increased cardiac sympathetic tone found in epilepsy will increase the risk for fatal cardiac arrhythmias and SUDEP. One recent case control study on SUDEP failed to identify unequivocal changes in HRV in SUDEP patients to allow for such predictions (Surges et al. 2009a) but this study had a small sample size and a more adequately powered study is required to study this possibility. An increase of

sympathetic tone in patients with intractable epilepsy has been suggested. Some studies mention heightened anxiety levels and others, decreased heart rate variability (Lee et al. 2009; Mukherjee et al. 2009). In addition, antiepileptic drug use and frequency of seizures have been identified to alter sympathetic cardiac autonomic function (Langan et al. 2005; Nei et al. 2010; Nilsson et al. 1999; Walczak et al. 2001). These are factors that are linked to prolonged medical history of epilepsy and substantiate the findings in this study. Normal diurnal variation in heart rate variability is characterized by the sleep related withdrawal of sympathetic tone (Bonnemeier et al. 2003; Cysarz et al. 2008; Hofstra et al. 2009). It has been suggested that this normal pattern would be disrupted in epilepsy patients (Persson et al. 2007b; Ronkainen et al. 2005), but this is not what I found in this study. Also previous studies in other patient groups in whom abnormal peripheral autonomic function was already established similarly did not find the HRV diurnal rhythm to be disrupted (Burger et al. 1999; Burger et al. 2001; Ewing et al. 1991; Kardelen et al. 2006; Malpas et al. 1990). In this study, with the exception of the sdnn (overall heart rate variability) I have shown a normal diurnal pattern of heart rate variability (Singh et al. 2003) in patients with epilepsy and this could mean that the night time occurrence of SUDEP may not be related to abnormalities in the HRV diurnal rhythm as has been suggested previously in epilepsy patients (Persson et al. 2007b; Ronkainen et al. 2005).

The lack of a statistical significant difference between mean day and night sdnn even though there is a normal diurnal pattern (see figure 18c), might be due to the large inter individual variability of heart rate variability. Furthermore, in the previous studies only patients with temporal lobe epilepsy on their full complement of antiepileptic drugs were investigated therefore the confounding effects on the HRV due to anticonvulsants and lobar location of epileptic focus (Hennessy et al. 2001; Tomson et al. 1998) could have affected the results. In this study I have found carbamazepine related polytherapy and left temporal lobe epilepsy to increase cardiac sympathetic activity independently of the day or night effect in line with the findings from earlier studies (Gelvan et al. 2001; Hennessy et al. 2001; Ide et al. 2007; Kenneback et al. 1997; Persson et al. 2003; Persson et al. 2007b; Ronkainen et al. 2005). A lower sympathetic tone is found in females in child bearing age group which approximates to the high levels in the male when the menopause is reached. Several explanations have been put forward including

methodological issues, cardioprotective female reproductive hormones and muscularity in the male (Bonnemeier et al. 2003; Kuo et al. 1999; Sztajzel et al. 2008). In this study also, the female patients were seen to have a lower sympathetic tone (Lower LF power). However they were seen to have higher mean heart rate. This discrepancy has been reported. The mean heart rate is often elevated when low frequency power HRV, a measure of sympathetic tone was reduced (Fitzgerald 2010; Sztajzel et al. 2008) and this may be the reason. Additionally in epilepsy, this could be due to the loss of the cardioprotective nature of estrogens (Verrotti et al. 2010). These and the other study findings show that HRV and the mean heart rate are not correlated and clinically significant changes in the HRV can occur without overt changes in the mean heart rate or vice versa. Increasing age has been known to decrease the HRV and increase sympathetic activity to the heart. It has been shown to be due a multitude of factors that include loss of vascular compliance, impaired integration of autonomic neural conduction and cardiac reflexes as well as sinoatrial node unresponsiveness. Impaired cardiovascular reflexes with aging are associated with increased serum norepinephrine levels. There is also evidence that with increasing age, an associated decrease of the intrinsic heart rate occurs because of impaired cardiac conduction and respiratory influences (Bonnemeier et al. 2003; Freeman et al. 2008; Hunt et al. 2001). These changes, the combined effects of increased serum levels of catecholamine in epilepsy and the apparent lack of correlation between HRV and the mean heart rate means that decreased HRV with prolonged history of epilepsy may be greater than the age related decrease of the HRV.

Hemispheric asymmetry of cardiac autonomic function in epilepsy has been previously described (Adjei et al. 2009; Assaf et al. 2008; Diehl et al. 1997; Evrengul et al. 2005; Oppenheimer et al. 1992). Right hemisphere related epilepsy enhances cardiac parasympathetic activity and left hemisphere related epilepsy enhances cardiac sympathetic function. The frontal lobe areas; ventromedial prefrontal area, orbitofrontal and anterior cingulate gyrus together with medial temporal lobe regions and insula; a deep cortical structure which is continuous with the temporal, parietal and frontal lobes represents cortical areas involved in central autonomic function and are also involved in epilepsy (Critchley et al. 2000). The insular cortex is of particular importance because it has been found to exert significant visceral autonomic function including heart rate

control and laterality in cardiac autonomic function. The insula is reciprocally connected to the temporal, frontal and parietal lobes as well as brainstem cardiovascular control centers. The inputs from the adjacent cortical areas are generally inhibitory to the ipsilateral insula functions and projections of the insula to the brainstem cardiovascular control centers (nucleus of the tractus solitarus) are also inhibitory. Cardiovascular sympatho-excitatory control is a right insula function and cardiac parasympathetic regulation is limited to the left insula (Oppenheimer 1993; Oppenheimer 2006; Oppenheimer 2007; Oppenheimer et al. 1996; Zhang et al. 2000a; Zhang et al. 2000b). Also FDG-PET studies have outlined interictal hypometabolism of the affected lobes in epilepsy (Lamusuo et al. 1997; Nelissen et al. 2006; Wong et al. 2010). The findings in this study are that there are asymmetries in cardiac autonomic control, and this may be explained by ipsilateral cortical dysfunction due to a right hemispheric epileptic focus which could lead to an enhanced inhibition of the ipsilateral insula and unopposed activity in the contra lateral parasympathetic insula and vice versa. Interestingly, in patients with temporal lobe epilepsy, there was no asymmetry between the HRV indices except in the LF/HF ratio. This may be one explanation for the difficulties in determining cortical representation of cardiac autonomic function in patients with epilepsy (Ahern et al. 2001; Jokeit et al. 2000). Furthermore, large inter individual variability in the location and in the extent of cortical representation of cardiac autonomic function, together with the extensive temporolimbic connections may underlie this finding.

The findings from these studies show that the impact of temporal lobe epilepsy on autonomic function is more marked than that of extratemporal lobe epilepsy as found by others (Harnod et al. 2009). Patients with temporal lobe epilepsy were found to have higher cardiac sympathetic tone. Interictal PET studies in temporal lobe epilepsy have shown extensive intratemporal and extratemporal hypofunction that involves the insula (Wong et al. 2010). Insula dysfunction releases inhibition on brainstem cardiovascular centers leading to unopposed cardiac sympathetic function (Oppenheimer 2006; Oppenheimer 2007). In light of this observation and as seen in this study, temporal lobe epilepsy may elevate cardiac sympathetic activity. This is not surprising given that autonomic symptoms in epilepsy are described most frequently in patients with temporal lobe epilepsy (Baumgartner et al. 2001).

Chapter 7

Catecholamines, electrolytes and cardiac troponin in seizures

Epileptic seizures are characterised by both systemic and central nervous system physiological changes that include generalised autonomic nervous system activation, a metabolic acidosis, and an increased central nervous system metabolism. During epileptic seizures, the accelerated release of adrenalin and noradrenalin affects the maintenance of electrolyte homeostasis. This favours the intracellular shift of potassium, calcium and magnesium. Catecholamine surge of such magnitude is a risk factor for cardiac myocardial dysfunction due to direct adreno-receptor vasoconstriction and myocardial toxicity (Clutter et al. 1980; Shimizu et al. 2008; Simon et al. 1984; Whitted et al. 2010). The intracellular shift of calcium creates hypocalcaemia. This stimulates parathormone which further worsens the intracellular loading. In cardiac myocytes, the accumulation increases oxidative stress and necrosis. Catecholamine based myocytic damage may release Troponin and eventual myocardial fibrosis which may serve as a nidus for arrhythmia (Lee et al. 2003; Ueshima et al. 2004; Whitted et al. 2010).

There are conflicting reports on the changes in serum sodium during epileptic seizures and in the interictal period (Hamed et al. 2004; Natelson et al. 1979a). Catecholamine induced hypokalaemia and hypomagnesaemia will prolong the QT interval and predispose to development of atrial fibrillations. Serum sodium is not known to be associated with QT interval changes; however a recent study identified significant QT interval prolongation with increased serum sodium (Lee et al. 2003; Sohaib et al. 2008). Therefore it is possible that the metabolic burden associated with epileptic seizures may facilitate the development of arrhythmias and myocardial ischemic injury. This is an area in epileptology that could help unravel the mechanisms of SUDEP.

7.1 Aim

The aim in this study was to test the hypothesis that epileptic seizures affect the serum concentration of adrenalin and noradrenalin, and the electrolytes (sodium, calcium, magnesium and potassium) and that these changes could impact on the corrected QT interval (QTc).

7.2 Methodology

Serum catecholamines, electrolytes and the corrected QT interval (Bazetts formula) were measured after seizures in chronic epilepsy patients. Refer chapter 3 section 3.4 for details.

7.3 Statistical Analysis

Linear mixed model analysis was used to evaluate the interaction between the electrolytes and QTc and between catecholamines and QTc. Refer to chapter 3 section 3.6 for details

7.4 Results

Summary of clinical characteristics

16 patients were included in this study. Three patients had secondary generalised tonic clonic seizures. All patients had drug reduction at the onset of the of the video telemetry investigation and were confused but not obviously agitated after cessation of the seizure. Clinical characteristics of all patients are presented in the table 7.1. Cardiac Troponin levels did not change in all seizure types after 12 hours. The changes in serum electrolytes are shown in tables 7.2-7.4. The changes in catecholamine levels are shown in tables 7.5-7.7. The interaction of catecholamines, electrolytes and the QTc interval during seizures is shown in table 7.8.

Table 7.1 Summary of Clinical characteristics (n=16)

Clinical characteristic	Observation
Age mean(SD) range/years	38(9)18-49
Gender M/F	12/4
Epilepsy duration mean(SD) range/years	24(11) 5-46
Seizure duration mean(SD) range /seconds	121(47) 50-190
Epileptic Focus Hemispheric location L/R	8/8
Lobar location TLE/FLE	9/7
Carbamazepine Polytherapy YES/NO	10/6

TLE temporal lobe epilepsy; FLE frontal lobe epilepsy

Electrolytes changes during seizures

Table7.2 Electrolytes data in the 3 time periods for all patients

Patient	Age	Epilepsy	Sex	Seizure	Na0 mmol/l	Na1 mmol/l	Na2 mmol/l	K0 mmol/l	K1 mmol/l	K2 mmol/l	Ca0 mmol/l	Ca1 mmol/l	Ca2 mmol/l	Mg0 mmol/l	Mg1 mmol/l	Mg2 mmol/l
1	47	LTLE	M	CPS	141	140	139	3.7	4.1	3.9	2.23	2.21	2.24	0.95	1.12	0.96
2	31	LTLE	M	CPS	135	138	138	4.2	4.1	4.3	2.41	2.39	2.41	0.99	1.14	1.09
3	32	RTLE	F	CPS	141	142	140	3.7	4.1	4.3	2.27	2.19	2.27	0.86	1.01	0.95
4	29	LTLE	F	CPS	144	141	141	4	3.7	3.9	2.38	2.29	2.29	0.86	0.91	0.88
5	37	LFLE	M	CPS	141	140	140	4.3	3.8	3.7	2.38	2.36	2.37	0.91	0.91	0.94
6	40	RTLE	M	CPS	138	141	141	4.9	3.9	4.6	2.34	2.26	2.42	0.93	0.91	0.86
7	43	LFLE	M	CPS	138	141	143	3.8	4.4	4.3	2.32	2.33	2.37	0.92	0.92	0.95
8	49	RFLE	M	CPS	140	141	140	4.4	4.5	4.2	2.23	2.20	2.27	0.91	0.89	0.86
9	46	RFLE	M	CPS	142	145	142	3.6	3.5	3.4	2.13	2.08	2.07	0.78	0.82	0.79
10	38	RFLE	M	CPS	138	142	140	4.2	3.9	4.6	2.26	2.21	2.30	0.82	0.9	0.87
11	26	LTLE	M	CPS	143	139	143	3.9	3.5	4.2	2.41	2.27	2.35	0.84	0.77	0.87
12	49	LTLE	F	GTCS	143	141	143	3.6	4.6	3.9	2.15	2.32	2.25	0.85	0.84	0.83
13	39	LFLE	F	GTCS	139	142	145	3.9	4.4	4.4	2.23	2.35	2.29	0.85	0.87	0.84
14	18	RFLE	M	GTCS	144	143	142	3.1	4.0	4.0	2.15	2.29	2.32	0.85	0.78	0.80
15	44	RTLE	M	CPS	141	145	144	4.4	4.2	4.6	2.27	2.32	2.27	0.82	0.80	0.90
16	43	RTLE	M	CPS	134	137	140	4.3	4.0	4.0	2.16	2.25	2.30	0.80	0.89	0.87

Na, K, Ca and Mg represent sodium, potassium, calcium and magnesium respectively. The numbers 0, 1 and 2 are the time periods: 0= baseline, 1= 5minutes postictal and 2= 12hours postictal. RTLE and LTLE: left and right frontal lobe epilepsy. RFLE and LFLE: right and left frontal lobe epilepsy. GTCS secondary generalized tonic clonic seizures CPS complex partial seizures. This shows very minor changes in the electrolytes which were not significant statistically (Table 7.3). All electrolytes were measured in mmol/l. The standard laboratory reference ranges of the electrolytes provided by the laboratory were: (Na^+=135mmol/l−145mmol/l, K^+=3.3mmol/l−4.7mmol/l, Ca^{2+}=2.12mmol/l – 2.62mmol/l and Mg^{2+}= 0.75mmol/l−1.0mmol/l).

The change in electrolytes from the baseline and 12 hours postictal was not statistically significant (Table 7.3).

Table 7.3 Change in electrolyte concentration with seizures

Electrolyte	Baseline serum level mmol/l	5 min postictal serum level/mmol/l	P Value	12 hours postictal serum level/mmol/l	P Value
Na^+	140(3) 134-144	141(2) 137-145	0.12	141(2) 138-145	0.062
K^+	4(0.4) 3.1-4.9	4.04(0.33) 3.5-4.6	0.69	4.14(0.34) 3.4-4.6	0.20
Ca^{2+}	2.27(0.1) 2.13-2.41	2.27(0.08) 2.08-2.39	1.0	2.30(0.08) 2.07-2.42	0.12
Mg^{2+}	0.87(0.06) 0.78-0.99	0.91(0.11) 0.77-1.14	0.034	0.89(0.07) 0.79-1.09	0.21

Overall there are no significant changes in the serum concentration of the electrolytes between the three time points. However, there is some evidence that there may be a change between the baseline and the 5minute postictal for mg (P=0.034). Results are reported as the mean (SD) range. The standard laboratory reference ranges of the electrolytes: (Na^+=135mmol/l−145mmol/l, K^+=3.3mmol/l−4.7mmol/l, Ca^{2+}=2.12mmol/l – 2.62mmol/l and Mg^{2+}= 0.75mmol/l−1.0mmol/l).

Overall, magnesium increases from base line by about 0.034mmol/l (P=0.034, 95%CI 0.002mmol/l to 0.065mmol/l). On average every second increase in the duration of the seizure decreases the serum concentration of the electrolytes magnesium by 0.0008mmol/l (P=0.018, 95%CI-0.0001mmol/l to -0.0015mmol/l) and potassium by 0.003mmol/l (P=0.039, 95%CI -0.0001mmol/l to -0.005mmol/l) after seizure type and change in time points have been adjusted for. On average, every second increase in the seizure duration, will increase the serum sodium by about 0.02 mmol/l (P=0.008, 95%CI 0.006mmol/l to 0.04mmol/l). The serum level of calcium is unaffected by seizures (P=1.00), seizure type (P=0.75) and seizure duration (P=0.25). The effect of seizure type on the serum concentration of the electrolytes are not statistically significant (Na^+: P=0.09), (K^+: P=0.77), (Ca^{2+}: P=0.75) and (Mg^{2+}: P=0.17).

Table 7.4 Results of electrolyte analysis

	Baseline vs. 5minute postictal			Baseline vs. 12 hours postictal			Generalised vs. Complex partial seizures			Seizure duration		
Variable	**Coef**	**P value**	**95% CI**	**Coef**	**P value**	**95% CI**	**Coef**	**P value**	**95% CI**	**Coef**	**P value**	**95% CI**
Na^+	1.00	0.12	-0.24 to 2.24	1.18	0.062	-0.06 to 2.43	1.59	0.09	-0.28 to3.47	0.02	0.008	0.006 to 0.4
K^+	0.04	0.69	-0.17 to 0.26	0.14	0.20	-0.77 to 0.36	-0.04	0.77	-0.35 to 0.26	-0.003	0.039	-0.005 to -0.0001
Ca^{2+}	$-5.96e^{-08}$	1.00	-0.36 to 0.36	0.029	0.12	-0.007 to 0.067	-0.015	0.75	-0.11 to 0.08	-0.0005	0.25	-0.001 to 0.0003
Mg^{2+}	0.034	0.034	0.002 to 0.065	0.02	0.21	-0.01 to 0.05	-0.05	0.17	-0.13 to 0.02	-0.008	0.18	-0.001 to 0.0001

Na^+, K^+, Ca^{2+} and Mg^{2+} are measured in mmol/l. The coefficients (Coef.) are the mathematical weighting of the effects of the explanatory variables on the outcome variable. A positive coefficient signifies an increasing effect on the outcome variable by the explanatory variable. The very small coefficient seen for calcium (-5.96e-08 is equivalent to 0) implies no change between baseline and 5minute postictal (P=1.0). CI: confidence intervals.

Catecholamine changes during seizures

Table 7.5 Catecholamine data in the 3 time periods for all Patients

Patient	Age	Epilepsy	Sex	Seizure	Noradrenalin (pg/ml)			Adrenalin (pg/ml)		
					0	1	2	0	1	2
1	47	LTLE	M	CPS	291	364	277	37	59	36
2	31	LTLE	M	CPS	313	343	326	57	79	57
3	32	RTLE	F	CPS	309	342	306	40	58	56
4	29	LTLE	F	CPS	215	315	191	38	109	37
5	37	LFLE	M	CPS	345	482	372	38	95	58
6	40	RTLE	M	CPS	313	363	313	38	57	37
7	43	LFLE	M	CPS	337	447	419	40	79	60
8	49	RFLE	M	CPS	356	394	324	37	74	36
9	46	RFLE	M	CPS	408	441	436	52	71	55
10	38	RFLE	M	CPS	324	336	294	46	59	43
11	26	LTLE	M	CPS	388	760	507	35	73	38
12	49	LTLE	F	GTCS	406	1453	440	57	165	55
13	39	LFLE	F	GTCS	473	642	574	57	174	59
14	18	RFLE	M	GTCS	456	727	642	43	146	42
15	44	RTLE	M	CPS	406	507	411	37	82	39
16	43	RTLE	M	CPS	591	913	575	40	82	42

Note that the noradrenalin change during generalized tonic clonic seizures are much higher than the normal reference ranges. The numbers 0, 1 and 2 are the time periods: 0= baseline, 1= 5minutes postictal and 2= 12hours postictal. RTLE and LTLE: left and right frontal lobe epilepsy. RFLE and LFLE: right and left frontal lobe epilepsy. GTCS secondary generalized tonic clonic seizures CPS complex partial seizures. Laboratory reference ranges provided are Adrenaline (<110 pg/ml) and Noradrenalin (70-500pg/ml)

Overall, the catecholamines increase significantly from the base line during seizures and returns to baseline by 12 hours postictal (Table 7.6).

Table 7.6 Mean catecholamine concentrations in the three time periods

Catecholamine	Baseline (pg/ml)	5 minute postictal(pg/ml)	12 hours postictal(pg/ml)
Noradrenalin	371(88)	552(299)	400(125)
Adrenalin	43(8)	91(38)	47(10)

Catecholamines increases to levels greater than the base line at the 5 minute postictal (NA & A: P<0.001 and P<0.001 respectively)

The result of the analysis indicate that from the baseline, there is a significant increase of about 181pg/ml for noradrenalin (P<0.001, 95%CI 79pg/ml to 283pg/ml) and 48pg/ml for adrenalin (P<0.001, 95% CI 35pg/ml to 60pg/ml). There is no difference between the baseline and 12hours postictal serum levels of the catecholamines (P=0.58 and 0.57 for adrenalin and noradrenalin respectively). On average, catecholamine increase is higher in secondary generalised tonic clonic seizures compared to complex partial seizures by about 252 pg/ml and 35pg/ml for noradrenalin and adrenalin respectively (noradrenalin: P=0.001, 95%CI 93pg/ml to 385pg/ml and adrenalin: P<0.001, 95%CI 21pg/ml to 49pg/ml). Unlike the electrolytes, prolonged seizure duration does not affect the serum level of the catecholamines (P= 0.22 and 0.54 for noradrenalin and adrenalin respectively).

Table 7.7 Results of Catecholamine analysis

	Noradrenalin			adrenalin		
Variable	**Coef.**	**P value**	**95%CI(pg/ml)**	**Coef.**	**P value**	**95%CI(pg/ml)**
5minute postictal vs. Baseline	181	<0.001	79 to 283	48	<0.001	35 to 60
12hours Postictal vs. Baseline	30	0.57	-72 to 132	4	0.58	-9 to 16
Partial vs. Generalised seizures	252	0.001	105 to 399	35	<0.001	21 to 49

The coefficients (Coef.) are the mathematical weighting of the effects of the explanatory variables on the outcome variable. A positive coefficient signifies an increasing effect on the outcome variable by the explanatory variable. CI: confidence intervals.

Table 7.8 Electrolytes and QTc in the preictal and postictal state for all patients

Patient	Timing of sampling	Na mmol/l	K mmol/l	Ca mmol/l	Mg mmol/l	A pg/ml	N pg/ml	QTc (s)
1	baseline	141	3.7	2.23	0.95	37	291	0.51
	5minutes postictal	140	4.1	2.21	1.12	59	364	0.53
2	baseline	135	4.2	2.41	0.99	57	313	0.53
	5minutes postictal	138	4.1	2.39	1.14	79	343	0.53
3	baseline	141	3.7	2.27	0.86	40	309	0.50
	5minutes postictal	142	4.1	2.19	1.01	58	342	0.51
4	baseline	144	4.0	2.38	0.86	38	215	0.49
	5minutes postictal	141	3.7	2.29	0.91	109	315	0.52
5	baseline	141	4.3	2.38	0.91	38	345	0.44
	5minutes postictal	140	3.8	2.36	0.91	95	482	0.43
6	baseline	138	4.9	2.34	0.93	38	313	0.45
	5minutes postictal	141	3.9	2.26	0.91	57	363	0.51
7	baseline	138	3.8	2.32	0.92	40	337	0.51
	5minutes postictal	141	4.4	2.33	0.92	79	447	0.57
8	baseline	140	4.4	2.23	0.91	37	356	0.48
	5minutes postictal	141	4.5	2.2	0.89	74	394	0.51
9	baseline	142	3.6	2.13	0.78	52	408	0.47
	5minutes postictal	145	3.5	2.08	0.82	71	441	0.47
10	baseline	138	4.2	2.26	0.82	46	324	0.45
	5minutes postictal	142	3.9	2.21	0.90	59	336	0.51
11	baseline	143	3.9	2.41	0.84	35	388	0.48
	5minutes postictal	139	3.5	2.27	0.77	73	760	0.57
12	baseline	143	3.6	2.15	0.85	57	406	0.59
	5minutes postictal	141	4.6	2.32	0.84	165	1453	0.44
13	baseline	139	3.9	2.23	0.85	57	473	0.46
	5minutes postictal	142	4.4	2.35	0.87	174	642	0.41
14	baseline	144	3.1	2.15	0.85	43	456	0.48
	5minutes postictal	143	4.0	2.29	0.78	146	727	0.44
15	baseline	141	4.4	2.27	0.82	37	406	0.47
	5minutes postictal	145	4.2	2.32	0.8	82	507	0.41
16	baseline	134	4.3	2.16	0.8	40	591	0.44
	5minutes postictal	137	4.0	2.25	0.89	82	913	0.49

Na, K, Ca, Mg, A, N and QTc represent Sodium mmol/l, potassium mmol/l, calcium mmol/l, magnesium mmol/l, adrenaline pg/ml, noradrenalin pg/ml and corrected QT interval (s).

Overall, mean QTc values at the baseline and 5 min postictally are the same (p=0.67), 0.48 (0.03) seconds and 0.49 (0.05) seconds respectively. However after checking for interaction of the peri-ictal concentrations of the electrolytes and catecholamines, QTc was higher than baseline by about 0.17s (P=0.001, 95%CI 0.07s to 0.27s) for adrenalin. Further analysis suggested that, whereas there was no linear relationship between QTc and the electrolytes at baseline, the 5 minute postictal concentrations of "Na^+" and "A" were seen to decrease the QTc interval by 0.014s (P=0.02, 95%CI -0.03s to -0.002s) and 0.009s (P<0.001, 95%CI -0.001s to -0.0003s) per 0.1mmol/l and 1pg/ml increase in the electrolyte and catecholamine respectively. The serum levels of the other electrolytes did not show this interaction at the 5minute postictal, with the QTc interval. However, overall, every one unit increase in serum level of K, Ca and noradrenalin, shortens the QTc interval by 0.05s (P=0.016, 95%CI -0.09s to -0.009s), 0.21s (P=0.027, 95%CI -0.41s to -0.025s) and 0.00008s (P=0.02, 95CI%-0.0002s to -0.00001s) respectively. When the serum concentration of magnesium increased by 0.1 mmol/l, the QTc interval increases by about 0.19s (P=0.041, 95%CI 0.008s to 0.37s).

7.5 Discussion

In summary, adrenaline and noradrenalin increases significantly during seizures which is still obvious in the 5 minute after the cessation of clinical seizure. The change in serum concentration of the electrolytes K, Na, and Ca with a seizure is not significant. However serum magnesium is increased with a seizure. When the seizure duration is increased, serum potassium and magnesium decreases, and serum sodium increases. There is a complex interaction of the catecholamines and the electrolytes with the QTc interval. Whereas the overall peri-ictal changes in concentration of serum adrenalin increase the QTc interval, at 5 minutes after the seizure, the changes in serum levels of sodium and adrenalin act to shorten the QTc interval. In addition rise in serum potassium, calcium and noradrenalin shortens the QTc interval and a rise in serum magnesium acts to prolong the QTc interval.

This study describes the elevation of serum catecholamines with seizures in agreement with the reports from previous studies (Aminoff et al. 1984; Simon et al. 1984). Five minutes after the cessation of clinical seizure activity, high levels of catecholamines are recorded. This shows that massive elevations of catecholamine occur during a seizure. Such sudden increases of catecholamines may have; 1) Direct adrenoceptor mediated myocardial damage and 2) indirect myocardial dysfunction through the changes in electrolyte homeostasis (Shimizu et al. 2008; Whitted et al. 2010). Increased serum adrenaline and noradrenalin such as may occur during epileptic seizures can generate hypokalaemia, hypomagnesaemia and hypocalcaemia. In this study, increasing hypokalaemia and hypomagnesaemia were observed with increasingly prolonged durations of a seizure. This effect may be due to ongoing epinephrine and norepinephrine induced intracellular influx of these ions. This is potentially important as hypokalaemia and hypomagnesaemia affect ventricular repolarisation by prolonging the QT interval. In contrast to other studies, I did not find any changes in serum calcium with seizures. Previous studies suggest a dynamic calcium homeostasis with seizures, with just before a seizure, hypocalcaemia attributed to hyperventilation related alkalosis and as the seizure progresses, the catecholamine surge further compromises the hypocalcaemia due to a catecholamine mediated intracellular loading. This study did not confirm these findings, although it is possible that with different timings of electrolyte

sampling and with a larger number of patients, a change in serum calcium might have been observed. However, unaltered calcium has been previously reported in the interictal phase in patients with epilepsy (Hamed et al. 2004; Natelson et al. 1979a). The finding of unchanged serum levels of sodium but increased sodium levels when the seizure is prolonged supports the findings of previous reports (Hamed et al. 2004; Natelson et al. 1979a; White et al. 1992). The change in serum magnesium during a seizure described in this study supports the work of Natelson (Natelson et al. 1979b). However with increased duration of seizures, serum magnesium was observed to fall. This may be attributable to elevated catecholamines which cause increased lipolysis and increased free fatty acid binding of magnesium together with cyclic AMP mediated intracellular loading of magnesium (Whitted et al. 2010). The clinical importance of hypomagnesaemia will be the likelihood for prolongation of the QT interval. However in this study when I attempted to evaluate the exact effect of serum magnesium on the corrected QT, no significant interactions were found.

Ventricular muscle repolarisation measured by the QT interval on the ECG has several properties. A change in autonomic tone modifies heart rate and cardiac muscle electrolyte handling through both neural and receptor mediated mechanisms. This affects the QT interval. In light of this the QT interval is adjusted for changes due to the heart rate [corrected QT (QTc)]. Some studies have suggested QTc to be prolonged in epilepsy (Neufeld et al. 2009; Surges et al. 2010). In this study also I have described increased QTc with epileptic seizures. Prolonged QTc is a risk for fatal cardiac arrhythmias and sudden death. The findings of the present study may provide a possible mechanism to explain some cases of SUDEP. In addition QTc shortening was also observed with increasing serum concentrations of the electrolytes and catecholamines. This is likely to be due to the increased heart rate (Neufeld et al. 2009). Furthermore, Bazette's squareroot formula can lead to signifcant over-correction and under-correction with small changes in the heart rate. Arguably, it is possible that over-correction at higher heart rates in the peri-ictal period, produced much less prolonged QTc interval. The cardiac Troponin did not change during both seizure types in contrast to earlier studies (Hajsadeghi et al. 2009; Woodruff et al. 2003). This may be due to the relative young age of the study subjects compared to that in the Woodruff study (2003) in which the subjects were elderly epilepsy patients with the additional risk for

atherosclerosis and myocardial ischemia. Additionally, multiple seizures and not single seizures have been reported to be associated with increased serum Troponin (Hajsadeghi et al. 2009) and it is not surprising that single seizures evaluated in this study were not associated with Troponin release.

Chapter 8

Limitations and Conclusion

8.1 Limitations

The studies described in this thesis have a number of limitations:

The lack of controls i.e. “newly diagnosed epilepsy patients” to match up with the chronic epilepsy cohort that this study group offers made it difficult to definitely assign the findings of abnormal interictal HRV as a consequence of epilepsy. I recommend any future study on the heart rate variability to be evaluated in both newly diagnosed and chronic epilepsy which would provide an unbiased relation between epilepsy and abnormal heart rate variability, although of course there will be significant practical difficulties in recording seizures in a newly diagnosed cohort. Equally the lack of a normal control population means that the extent of the abnormalities (for instance changes of HRV with prolonged medical history of epilepsy) cannot be easily assessed.

For study chapter 4, the major limitation identified in this study is the biological significance of the SDNN derived from the 10 second ECG recording. Further studies could help provide greater understanding into its clinical utility. Nevertheless it was useful in evaluating the HRV during epileptic seizures because of the highly variable length of seizures and the fact that 10 seconds segments would be generally devoid of movement of artefacts. Power spectral analysis on the ictal ECG segments in study chapter 5 would have help outline the spectral components of the ECG segment. However, this analysis requires the use of a minimum of 2 minutes ECG segments and this is practically impossible in seizures. Almost all simultaneous ECG recording during seizures have movement artefacts which may render large segments of ECG unusable for RR interval analysis. This allows us to revisit the issue of further studies to delineate the clinical significance of 10 second segments of ECG in RR interval analysis.

In study chapter 6, I have used 12 hour blocks for the day and night. This may not be physiological considering the geographic location of the patients and I cannot rule out the effects it could have had on the results. The patients were either incumbent or

supine for most part of the day during data acquisition and I probably measured only the resting heart rate and its variability which is controlled by vagal efferent activity. However previously published studies have established the HRV is not affected by posture (Ewing et al. 1991). But since this is only one report and have not been replicated in other studies, the effects of this on the results cannot be entirely overruled. I have also utilised multiple recordings per patient over 24 hours and even though a robust statistical method that takes into account the correlation between the multiple measures per person(Hanley et al. 2003) was used, large sample bias could still have been introduced.

In the study chapter 7, electrolytes and catecholamines were determined in the immediate postictal period because of ethical and technical constraints. The earliest time after the seizure, which was chosen to be 5 minutes in this study could have missed transient and crucial changes in the electrolytes during and immediately after the seizure. In addition the small data set may have introduced small sample bias in the results. Nevertheless significant finding that corroborate earlier reports have been amply described and these can serve to direct future studies on this subject.

An experiment to determine whether the changes in skin resistance during a seizure can be used as an index of sympathetic function during seizures was started. In all 10 patients were recruited. Adhesive skin contacts electrodes were placed on the hypothenar and dorsal surfaces of the palms on either side after preparing the skin surface with commercially available skin prep gel. Two skin resistance channels were thus produced and these were connected to the Nicolet one EEG amplifier used for the acquisition of electrophysiological data. Different filter settings were applied to these channels (LFF=0.5Hz and HFF=5Hz). However, this was abandoned due to limitations in the experimental procedure such as;

- The inability of the electrodes to keep because of sweatiness of palms or the movements of the hands during the acquisition of data.
- Technical and logistic difficulties that demanded the constant electrode management.
- Introduction of EEG artefact in skin channel and multiple deflections of skin voltage that were not related to the occurrence of seizures.

8.2 Conclusions

The major conclusions that can be drawn from the studies in this thesis are;

1. Subclinical seizures (electrographic seizures without clinical accompaniment) do not alter heart rate variability. Subclinical seizures are highly localised and it is possible that acute cardiovascular autonomic dysfunction will not occur when the ictal discharges do not spread to brain areas controlling autonomic function. This finding is in accord with the view that any change in heart rate variability in subclinical seizures most likely indicates ictal discharges in the insula and other parts of the central autonomic network such as the hypothalamus and the medullary cardiovascular centres.

2. During overt seizures (clinical seizures), the heart rate variability decreases and it is seen to return to the pre seizure state within 20 seconds after the cessation of electrographic activity. This sudden and precipitous decrease of the heart rate variability reduces the resilience of the heart to respond to rate and rhythm changes. This could unmask rhythm and mechanical abnormalities in persons with and without latent cardiac disease and sudden death. This is an important finding that could provide a possible mechanism for SUDEP.

3. An epileptic seizure irrespective of the hemispheric side and location decreases the heart rate variability and increases the mean heart rate. Therefore heart rate variability estimated during the ictal period cannot be used to accurately localise and or lateralise the epileptic focus in the cerebral cortex during presurgical evaluation.

4. Intractable epilepsy does not disrupt the circadian rhythm of the heart rate variability. However, the heart rate variability in epilepsy patients decreases for every year the patient has intractable epilepsy which is independent of age related changes in the heart rate variability. Depressed heart rate variability is an independent risk factor that can help to predict mortality due to cardiac arrhythmia. Therefore, this may mean the epilepsy patient is at an increased risk of fatal arrhythmias.

5. Epileptic seizures increases serum concentrations of adrenalin, noradrenalin, magnesium and the corrected QT interval but have no effects on the serum potassium, sodium and calcium. The increased catecholamine and the associated cardiac repolarisation abnormalities might be a mechanism for SUDEP.

Other conclusions that can be drawn from this study are:

6. Female patients with epilepsy have lower cardiac sympathetic tone compared to their male counterparts in the interictal state.

7. High seizure frequency and antiepileptic polytherapy with carbamazepine based regimen may increase the cardiac sympathetic tone.

8. The effects of aging on HRV alone may not be responsible for the decrease in HRV associated with prolonged medical history of epilepsy.

9. There is asymmetry of central cardiac autonomic function in the interictal period. Right hemispheric lesions increase parasympathetic activity to the heart and left hemispheric lesion stimulate cardiac sympathetic activity.

10. Temporal lobe epilepsy is particularly associated with higher cardiac sympathetic tone.

11. The age, gender, duration of epileptic seizure, carbamazepine related antiepileptic drug polytherapy and the epilepsy duration do not affect the ictal change in HRV.

12. The prolonged seizure duration will not affect the level of catecholamine increase in serum but significantly changes the serum electrolyte concentrations.

What is the significance of the findings in this study in relation to heart rate variability in epilepsy? Firstly, heart rate variability is substantially affected in intractable epilepsy in both the ictal and interictal period. Reduced HRV means an increased cardiac sympathetic tone and this implies that in epilepsy there may be an enhanced risk of ventricular arrhythmias and sudden cardiac death. Given the prognostic and risk predictive power of the HRV on fatal arrhythmias and the fact that people with epilepsy have a higher mortality compared to the general population, these findings point to an important potential mechanism in the production of SUDEP. The question now is could the HRV in epilepsy patients be modified by the use of cardioprotective measures such as beta blocker therapy, antiarrhythmic drugs and exercise training? This has been suggested in post myocardial infarction patients who have much reduced HRV. This offers a potential opportunity to provide protection against SUDEP. Secondly, there is really no correlation between the HRV and mean heart rate. Very significant HRV abnormalities can occur despite relative normal mean heart rates. I suggest therefore that methods to evaluate heart rate variability should be incorporated in the clinical care of patients with intractable epilepsy. By so doing epilepsy patients at risk of cardiac autonomic dysfunction could be identified and treatments provided with the aim to improve cardiac autonomic activity.

Finally, the findings emphasise the further benefits of strict control of seizures in epilepsy because of the detrimental effects of the significant physiologic changes that occur in seizures. Overall this thesis confirms that epilepsy is associated with altered cardiac autonomic dysfunction. A common finding is the reduced heart rate variability which is identical to that which occurs in other patient groups at major risk for sudden cardiac death. The responsible factors for the reduced HRV include, prolonged medical history of epilepsy, the cortical pathology itself, seizures and their frequency and the antiepileptic drug treatment. There may be other factors yet to be identified. The practical importance of these findings is that they provide a plausible explanation for at least some cases of SUDEP, both in ictally-related and also in non ictally-related cases.

8.3 Future directions

Possibilities for future studies of the heart rate variability in epilepsy that arise from this work are:

1. Longitudinal HRV studies in newly diagnosed epileptics for prolonged periods of follow ups to determine beyond any reasonable doubt the extent to which the reduction in HRV is progressive in epilepsy patients. This provides one explanation for the observation that the risk of SUDEP is greater the more prolonged is the history of epilepsy. Any such study should include the carbamazepine vs. non carbamazepine treated groups and the seizure frequency per year.

2. Longitudinal controlled experiment in intractable epilepsy patients in which the effect of specific interventions designed to modify HRV will be studied. The experimental group will have HRV modification interventions and the effects should be compared to a control group in whom no interventions were carried out. Changes in HRV (and SUDEP rates if this is possible to ascertain) should be compared in both groups, at specified follow-up intervals.

3. Further detailed electrolyte studies in both clinical and experimental epilepsy. This should detail the sampling of blood for analysis closer to the offset of seizures and if possibly during the seizure in the case of experimental epilepsy. Serum changes with multiple seizures should be compared and this could help unravel changes in the plasma electrolytes during seizures.

4. Longitudinal studies on the measurement of QTc interval before and immediately after epileptic seizures will help confirm whether QTc prolongation become evident after epileptic seizures.

5. Study/studies that will develop a more robust method for evaluating the skin resistance during seizures may help to evaluate sympathetic activity during seizures.

6. Direct studies of SUDEP- Large scale studies in patients who have subsequently died in SUDEP such as the MORTEMUS should incorporate evaluation of the HRV in the study design because the association of reduced HRV in epileptic patient's could have very important implications for SUDEP.

Bibliography

Adjei, P., Surges, R., Scott, C.A., Kallis, C., Shorvon, S., & Walker, M.C. 2009. Do subclinical electrographic seizure patterns affect heart rate and its variability? *Epilepsy Research*, 87, (2-3) 281-285.

Ahern GL, Sollers JJ, Lane RD, Labiner DM, Herring AM, Weinand ME, Hutzler R, Thayer JF. 2001. Heart rate and heart rate variability changes in the intracarotid sodium amobarbital test. *Epilepsia*, 42, 912-21.

Ahmed, S.N. 2005. Epileptic seizures and epilepsy. *Epilepsia*, 46, (10) 1700-1701.

Aminoff, M.J., Simon, R.P., & Wiedemann, E. 1984. The hormonal responses to generalized tonic-clonic seizures. *Brain*, 107 (Pt 2), 569-578.

Anand, B.K. & Dua, S. 1956. Circulatory and respiratory changes induced by electrical stimulation of limbic system (visceral brain). *Journal of Neurophysiology*, 19, (5) 393-400.

Ansakorpi, H., Korpelainen, J.T., Huikuri, H.V., Tolonen, U., Myllyla, V.V., & Isojarvi, J.I. 2002a. Heart rate dynamics in refractory and well controlled temporal lobe epilepsy. *Journal of Neurology, Neurosurgery and Psychiatry*, 72, (1) 26-30.

Ansakorpi, H., Korpelainen, J.T., Huikuri, H.V., Tolonen, U., Myllyla, V.V., & Isojarvi, J.I. 2002b. Heart rate dynamics in refractory and well controlled temporal lobe epilepsy. *Journal of Neurology, Neurosurgery and Psychiatry*, 72, (1) 26-30.

Ansakorpi, H., Korpelainen, J.T., Suominen, K., Tolonen, U., Myllyla, V.V., & Isojarvi, J.I. 2000. Interictal cardiovascular autonomic responses in patients with temporal lobe epilepsy. *Epilepsia*, 41, (1) 42-47.

Assaf, N., Weller, B., Deutsh-Castel, T., Cohen, A., & Tirosh, E. 2008. The relationship between heart rate variability and epileptiform activity among children--a controlled study. *Journal of Clinical Neurophysiology*, 25, (5) 317-320.

Athwal, B.S., Berkley, K.J., Hussain, I., Brennan, A., Craggs, M., Sakakibara, R., Frackowiak, R.S., & Fowler, C.J. 2001. Brain responses to changes in bladder volume and urge to void in healthy men. *Brain*, 124, (Pt 2) 369-377.

Bannister, R. & Mathias CJ 1988, "Testing Autonomic Reflexes," *In Autonomic Failure: A Textbook of Clinical Disorders of the Autonomic Nervous System*, 2nd ed. R. Bannister & Mathias CJ, eds., London: Oxford University Press, pp. 289-307.

Bannister, R. & Mathias CJ 1999, "Clinical Features and Evaluation of the Primary Chronic Autonomic Failure Syndromes," *In A Textbook of Clinical Disorders of the Autonomic Nervous System*, 4th ed. R. Bannister & Mathias CJ, eds., New York: Oxford University Press, pp. 307-316.

Barron, K. D. & Chokroverty, S. 1993, "Anatomy of the Autonomic Nervous System:Brain and Brainstem," *In Clinical Autonomic Disorders :Evalaution and Management*, 1st ed. P. A. Low, ed., Rochester Minnesota: Mayo Foundation, pp. 3-14.

Baumgartner, C., Groppel, G., Leutmezer, F., Aull-Watschinger, S., Pataraia, E., Feucht, M., Trinka, E., Unterberger, I., & Bauer, G. 2000. Ictal urinary urge indicates seizure onset in the nondominant temporal lobe. *Neurology*, 55, (3) 432-434.

Baumgartner, C., Lurger, S., & Leutmezer, F. 2001. Autonomic symptoms during epileptic seizures. *Epileptic Disorders*, 3, (3) 103-116.

Bear, D., Schenk, L., & Benson, H. 1981. Increased autonomic responses to neutral and emotional stimuli in patients with temporal lobe epilepsy. *American Journal of Psychiatry*, 138, (6) 843-845.

Bennaroch, E. E. 1997, "Telencephalic Disorders," *In Central Autonomic Network:Functional Organisation and Clinical Correlation*, New York: Futura Publications Company Inc, pp. 539-559.

Bennaroch, E. E. 2007, The Autonomic Nervous System: Basic Anatomy and Physiology. Continuum: Lifelong Learning in Neurology 13[6(Autonomic Disorders)], 13-32.

Bergen, D. & Ristanovic, R. 1993. Weeping as a common element of pseudoseizures. *Archives of Neurology*, 50, (10) 1059-1060.

Billman, G.E., McIlroy, B., & Johnson, J.D. 1991. Elevated myocardial calcium and its role in sudden cardiac death. *FASEB Journal*, 5, (11) 2586-2592.

Binnie, C.D. 2003. Cognitive impairment during epileptiform discharges: is it ever justifiable to treat the EEG? *Lancet Neurol.*, 2, (12) 725-730.

Blum, A.S., Ives, J.R., Goldberger, A.L., Al-Aweel, I.C., Krishnamurthy, K.B., Drislane, F.W., & Schomer, D.L. 2000. Oxygen desaturations triggered by partial seizures: implications for cardiopulmonary instability in epilepsy. *Epilepsia*, 41, (5) 536-541.

Blumhardt, L.D., Smith, P.E., & Owen, L. 1986. Electrocardiographic accompaniments of temporal lobe epileptic seizures. *Lancet*, 1, (8489) 1051-1056.

Bonnemeier, H., Richardt, G., Potratz, J., Wiegand, U.K., Brandes, A., Kluge, N., & Katus, H.A. 2003. Circadian profile of cardiac autonomic nervous modulation in healthy subjects: differing effects of aging and gender on heart rate variability. *Journal of Cardiovascular Electrophysiology*, 14, (8) 791-799.

Brenner, R.P. 1997. Electroencephalography in syncope. *Journal of Clinical Neurophysiology*, 14, (3) 197-209.

Brown, R.W. & McLeod, W.R. 1973. Sympathetic stimulation with temporal lobe epilepsy. *Medical Journal of Australia*, 2, (6) 274-276.

Burger, A.J. & Aronson, D. 2001. Effect of diabetes mellitus on heart rate variability in patients with congestive heart failure. *Pacing and Clinical Electrophysiology*, 24, (1) 53-59.

Burger, A.J., Charlamb, M., & Sherman, H.B. 1999. Circadian patterns of heart rate variability in normals, chronic stable angina and diabetes mellitus. *International Journal of Cardiology*, 71, (1) 41-48.

Calkins, H., Shyr, Y., Frumin, H., Schork, A., & Morady, F. 1995. The value of the clinical history in the differentiation of syncope due to ventricular tachycardia, atrioventricular block, and neurocardiogenic syncope. *American Journal of Medicine*, 98, (4) 365-373.

Cannon, W.B. 2002. "Voodoo" death. American Anthropologist, 1942;44(new series):169-181. *American Journal of Public Health*, 92, (10) 1593-1596.

Carinci, V., Barbato, G., Baldrati, A., & Di, P.G. 2007. Asystole induced by partial seizures: a rare cause of syncope. *Pacing and Clinical Electrophysiology*, 30, (11) 1416-1419.

Carrington, M., Walsh, M., Stambas, T., Kleiman, J., & Trinder, J. 2003. The influence of sleep onset on the diurnal variation in cardiac activity and cardiac control. *Journal of Sleep Research*, 12, (3) 213-221.

Castle, M., Comoli, E., & Loewy, A.D. 2005. Autonomic brainstem nuclei are linked to the hippocampus. *Neuroscience*, 134, (2) 657-669.

Catenoix, H., Isnard, J., Guenot, M., Petit, J., Remy, C., & Mauguiere, F. 2008. The role of the anterior insular cortex in ictal vomiting: a stereotactic electroencephalography study. *Epilepsy Behav.*, 13, (3) 560-563.

Cechetto, D.F. & Saper, C.B. 1988. Neurochemical organization of the hypothalamic projection to the spinal cord in the rat. *J.Comp Neurol.*, 272, (4) 579-604.

Cerullo, A., Tinuper, P., Provini, F., Contin, M., Rosati, A., Marini, C., & Cortelli, P. 1998. Autonomic and hormonal ictal changes in gelastic seizures from hypothalamic hamartomas. *Electroencephalography and Clinical Neurophysiology*, 107, (5) 317-322.

Chokroverty, S. 2008, "Sleep and Its Disorders," *In Neurology in Clinical Practice*, 5th ed. vol. 2 Bradley WG et al., eds., Philadelphia: Butterworth Heinemann Elsevier, pp. 1947-2009.

Chroni, E., Sirrou, V., Trachani, E., Sakellaropoulos, G.C., & Polychronopoulos, P. 2009. Interictal alterations of cardiovagal function in chronic epilepsy. *Epilepsy Research*, 83, (2-3) 117-123.

Clutter, W.E., Bier, D.M., Shah, S.D., & Cryer, P.E. 1980. Epinephrine plasma metabolic clearance rates and physiologic thresholds for metabolic and hemodynamic actions in man. *J.Clin.Invest*, 66, (1) 94-101.

Colice, G.L., Matthay, M.A., Bass, E., & Matthay, R.A. 1984. Neurogenic pulmonary edema. *American Review of Respiratory Disease*, 130, (5) 941-948.

Constantin, L., Martins, J.B., Fincham, R.W., & Dagli, R.D. 1990. Bradycardia and syncope as manifestations of partial epilepsy. *Journal of the American College of Cardiology*, 15, (4) 900-905.

Cook, M. 2009, "Differential Diagnosis of Epilepsy," *In The Treatment of Epilepsy*, 3rd ed. Simon Shorvon, Emilio Perucca, & Jerome Engel Jr, eds., Singapore: Blackwell Publishing Ltd, pp. 55-66.

Cooke, W.H., Cox, J.F., Diedrich, A.M., Taylor, J.A., Beightol, L.A., Ames, J.E., Hoag, J.B., Seidel, H., & Eckberg, D.L. 1998. Controlled breathing protocols probe human autonomic cardiovascular rhythms. *Am.J.Physiol*, 274, (2 Pt 2) H709-H718.

Coulter, D.L. 1984. Partial seizures with apnea and bradycardia. *Archives of Neurology*, 41, (2) 173-174.

Crawford, P. 2005. Best practice guidelines for the management of women with epilepsy. *Epilepsia*, 46 Suppl 9, 117-124.

Critchley, H.D., Corfield, D.R., Chandler, M.P., Mathias, C.J., & Dolan, R.J. 2000. Cerebral correlates of autonomic cardiovascular arousal: a functional neuroimaging investigation in humans. *J.Physiol*, 523 Pt 1, 259-270.

Cropp, G.J. & Manning, G.W. 1960. Electrocardiographic changes simulating myocardial ischemia and infarction associated with spontaneous intracranial hemorrhage. *Circulation*, 22, 25-38.

Cysarz, D., von, B.D., Brachmann, P., Buetler, S., Edelhauser, F., Laederach-Hofmann, K., & Heusser, P. 2008. Day-to-night time differences in the relationship between cardiorespiratory coordination and heart rate variability. *Physiol Meas.*, 29, (11) 1281-1291.

Darbin, O., Casebeer, D.J., & Naritoku, D.K. 2002. Cardiac dysrhythmia associated with the immediate postictal state after maximal electroshock in freely moving rat. *Epilepsia*, 43, (4) 336-341.

De Bruyne, M.C., Kors, J.A., Hoes, A.W., Klootwijk, P., Dekker, J.M., Hofman, A., van Bemmel, J.H., & Grobbee, D.E. 1999. Both decreased and increased heart rate variability on the standard 10-second electrocardiogram predict cardiac mortality in the elderly: the Rotterdam Study. *American Journal of Epidemiology*, 150, (12) 1282-1288.

De Vincentiis, S., Febronio, M.V., Da Silva, C.A., Saito, M.I., Takiuti, A.D., & Valente, K.D. 2008. Sexuality in teenagers with epilepsy. *Epilepsy Behav.*, 13, (4) 703-706.

Delgado, J.M., MIHAILOVIC, L., & Sevillano, M. 1960. Cardiovascular phenomena during seizure activity. *Journal of Nervous and Mental Disease*, 130, 477-487.

Demerdash, A., Shaalan, M., Midani, A., Kamel, F., & Bahri, M. 1991. Sexual behavior of a sample of females with epilepsy. *Epilepsia*, 32, (1) 82-85.

Devinsky, O. 2004. Effects of Seizures on Autonomic and Cardiovascular Function. *Epilepsy Curr.*, 4, (2) 43-46.

Devinsky, O., Frasca, J., Pacia, S.V., Luciano, D.J., Paraiso, J., & Doyle, W. 1995. Ictus emeticus: further evidence of nondominant temporal involvement. *Neurology*, 45, (6) 1158-1160.

Devinsky, O., Perrine, K., & Theodore, W.H. 1994. Interictal autonomic nervous system function in patients with epilepsy. *Epilepsia*, 35, (1) 199-204.

Devinsky, O., Price, B.H., & Cohen, S.I. 1986. Cardiac manifestations of complex partial seizures. *American Journal of Medicine*, 80, (2) 195-202.

Di, G.G., Quarato, P.P., Sebastiano, F., Esposito, V., Onorati, P., Grammaldo, L.G., Meldolesi, G.N., Mascia, A., Falco, C., Scoppetta, C., Eusebi, F., Manfredi, M., & Cantore, G. 2004. Ictal heart rate increase precedes EEG discharge in drug-resistant mesial temporal lobe seizures. *Clinical Neurophysiology*, 115, (5) 1169-1177.

Diehl, B., Diehl, R.R., Stodieck, S.R., & Ringelstein, E.B. 1997. Spontaneous oscillations in cerebral blood flow velocities in middle cerebral arteries in control subjects and patients with epilepsy. *Stroke*, 28, (12) 2457-2459.

Doba, N., Beresford, H.R., & Reis, D.J. 1975. Changes in regional blood flow and cardiodynamics associated with electrically and chemically induced epilepsy in cat. *Brain Research*, 90, (1) 115-132.

Dobesberger, J., Walser, G., Unterberger, I., Embacher, N., Luef, G., Bauer, G., Benke, T., Bartha, L., Ulmer, H., Ortler, M., & Trinka, E. 2004. Genital automatisms: a video-EEG study in patients with medically refractory seizures. *Epilepsia*, 45, (7) 777-780.

Drake, M.E. 1984. Isolated ictal autonomic symptoms in complex partial seizures. *Journal of Neurology, Neurosurgery and Psychiatry*, 47, (1) 100-101.

Druschky, A., Hilz, M.J., Hopp, P., Platsch, G., Radespiel-Troger, M., Druschky, K., Kuwert, T., Stefan, H., & Neundorfer, B. 2001. Interictal cardiac autonomic dysfunction in temporal lobe epilepsy demonstrated by [(123)I]metaiodobenzylguanidine-SPECT. *Brain*, 124, (Pt 12) 2372-2382.

Dutsch, M., Hilz, M.J., & Devinsky, O. 2006. Impaired baroreflex function in temporal lobe epilepsy. *Journal of Neurology*, 253, (10) 1300-1308.

Earnest, M.P., Thomas, G.E., Eden, R.A., & Hossack, K.F. 1992. The sudden unexplained death syndrome in epilepsy: demographic, clinical, and postmortem features. *Epilepsia*, 33, (2) 310-316.

Eisalo, A., Perasalo, J., & Halonen, P.I. 1972. Electrocardiographic abnormalities and some laboratory findings in patients with subarachnoid haemorrhage. *British Heart Journal*, 34, (3) 217-226.

El-Sayed, H.L., Kotby, A.A., Tomoum, H.Y., El-Hadidi, E.S., El Behery, S.E., & El-Ganzory, A.M. 2007. Non-invasive assessment of cardioregulatory autonomic functions in children with epilepsy. *Acta Neurologica Scandinavica*, 115, (6) 377-384.

Engel, J. & Pedley, T. A. 2008, "Introduction:What is Epilepsy?," *In Epilepsy A Comprehensive Textbook*, Second ed. J. Engel & T. A. Pedley, eds., Philadelphia: Wolters Kluwer, Lippincott Williams&Wilkins, pp. 1-11.

Epstein, M.A., Sperling, M.R., & O'Connor, M.J. 1992. Cardiac rhythm during temporal lobe seizures. *Neurology*, 42, (1) 50-53.

Eross, L., Entz, L., Fabo, D., Jakus, R., Szucs, A., Rasonyi, G., Kelemen, A., Barcs, G., Juhos, V., Balogh, A., Barsi, P., Clemens, Z., & Halasz, P. 2009. Interhemispheric propagation of seizures in mesial temporal lobe epilepsy. *Ideggyogy.Sz*, 62, (9-10) 319-325.

Evrengul, H., Tanriverdi, H., Dursunoglu, D., Kaftan, A., Kuru, O., Unlu, U., & Kilic, M. 2005. Time and frequency domain analyses of heart rate variability in patients with epilepsy. *Epilepsy Research*, 63, (2-3) 131-139.

Ewing, D.J., Neilson, J.M., Shapiro, C.M., Stewart, J.A., & Reid, W. 1991. Twenty four hour heart rate variability: effects of posture, sleep, and time of day in healthy controls and comparison with bedside tests of autonomic function in diabetic patients. *British Heart Journal*, 65, (5) 239-244.

Faustmann, P.M. & Ganz, R.E. 1994. Central cardio-autonomic disorganization in interictal states of epilepsy detected by phase space analysis. *International Journal of Neuroscience*, 78, (1-2) 43-47.

Fenichel, G.M., Olson, B.J., & Fitzpatrick, J.E. 1980. Heart rate changes in convulsive and nonconvulsive neonatal apnea. *Annals of Neurology*, 7, (6) 577-582.

Fisher, R.S., van Emde, B.W., Blume, W., Elger, C., Genton, P., Lee, P., & Engel, J., Jr. 2005. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia*, 46, (4) 470-472.

Fitzgerald, M. J. T., Greuner G, & Mtui E 2007a, "Autonomic Nervous system and visceral afferents," *In Clinical Neuroanatomy and Neuroscience*, 5th ed. Elsevier Saunder, pp. 151-168.

Fitzgerald, M. J. T., Greuner G, & Mtui E 2007b, "Hypothalamus," *In Clincal Neuroanatomy and Neuroscience*, 5th ed. Elsevier Saunder, pp. 289-295.

Fitzgerald, M. J. T., Greuner G, & Mtui E 2007c, "Olfactory and Limbic system," *In Clinical Neuroanatomy and Neuroscience*, 5th ed. Elsevier Saunder, pp. 367-390.

Fitzgerald, P.J. 2010. Is elevated norepinephrine an etiological factor in some cases of epilepsy? *Seizure.*, 19, (6) 311-318.

Flachenecker, P., Hartung, H.P., & Reiners, K. 1997. Power spectrum analysis of heart rate variability in Guillain-Barre syndrome. A longitudinal study. *Brain*, 120 (Pt 10), 1885-1894.

Fleisher, D.R. & Morrison, A. 1990. Masturbation mimicking abdominal pain or seizures in young girls. *Journal of Pediatrics*, 116, (5) 810-814.

Fogarasi, A., Janszky, J., & Tuxhorn, I. 2007. Ictal emotional expressions of children with partial epilepsy. *Epilepsia*, 48, (1) 120-123.

Freeman, R. 2006. Cardiovascular manifestations of autonomic epilepsy. *Clinical Autonomic Research*, 16, (1) 12-17.

Freeman, R. & Schachter, S.C. 1995. Autonomic epilepsy. *Seminars in Neurology*, 15, (2) 158-166.

Freeman, R. L. 2008, "Noninvasive Evaluation of Heart Rate," *In Clinical Autonomic Disorders*, 3 ed. P. A. Low & E. E. Bennaroch, eds., Philadelphia: Lippincott Williams & Wilkins, pp. 185-195.

Freeman, R. L. & Bennaroch, E. E. 2008, "Autonomic Manifestations of Epilepsy and Stroke," *In Clinical Autonomic Disorders*, 3rd ed. Phillip A Low & E. E. Bennaroch, eds., Philadelphia: Lippincott William & Wilkins, pp. 345-355.

Frysinger, R.C., Engel, J., & Harper, R.M. 1993. Interictal heart rate patterns in partial seizure disorders. *Neurology*, 43, (10) 2136-2139.

Furlan, R., Guzzetti, S., Crivellaro, W., Dassi, S., Tinelli, M., Baselli, G., Cerutti, S., Lombardi, F., Pagani, M., & Malliani, A. 1990. Continuous 24-hour assessment of the neural regulation of systemic arterial pressure and RR variabilities in ambulant subjects. *Circulation*, 81, (2) 537-547.

Garcia, M., D'Giano, C., Estelles, S., Leiguarda, R., & Rabinowicz, A. 2001. Ictal tachycardia: its discriminating potential between temporal and extratemporal seizure foci. *Seizure.*, 10, (6) 415-419.

Gelvan, A. & Pallisgaard, G. 2001. Carbamazepine induced right bundle branch block in a Greenlandic patient. *Int.J.Circumpolar.Health*, 60, (3) 407-410.

Ghearing, G.R., Munger, T.M., Jaffe, A.S., Bennaroch, E.E., & Britton, J.W. 2007. Clinical cues for detecting ictal asystole. *Clinical Autonomic Research*, 17, (4) 221-226.

Gil-Nagel, A. & Risinger, M.W. 1997. Ictal semiology in hippocampal versus extrahippocampal temporal lobe epilepsy. *Brain*, 120 (Pt 1), 183-192.

Giorgi, F.S., Pizzanelli, C., Biagioni, F., Murri, L., & Fornai, F. 2004. The role of norepinephrine in epilepsy: from the bench to the bedside. *Neuroscience and Biobehavioral Reviews*, 28, (5) 507-524.

Goldstein, D.S. & Low, P.A. 2007. Clinical Evaluation of the Autonomic Nervous System. *Continuum: Lifelong Learning in Neurology*, 13, (6) 33-49.

Gomez-Alonso, J., Andrade, C., & Koukoulis, A. 2005. On the definition of epileptic seizures and epilepsy. *Epilepsia*, 46, (10) 1699-1700.

Goodman, J. H., Stewart M, & Drislane FW 2008, "Autonomic Disturbances," *In Epilpesy, A Comprehensive Textbook*, 2nd ed. vol. 3 Engel & Pedley, eds., Lippincott William & Wilkins, pp. 1999-2005.

Gupta, A.K., Jeavons, P.M., Hughes, R.C., & Covanis, A. 1983. Aura in temporal lobe epilepsy: clinical and electroencephalographic correlation. *Journal of Neurology, Neurosurgery and Psychiatry*, 46, (12) 1079-1083.

Hajsadeghi, S., Afsharian, S., Fereshtehnejad, S.M., Keramati, M.R., & Mollahoseini, R. 2009. Serum levels of cardiac troponin I in patients with uncomplicated epileptic seizure. *Archives of Medical Research*, 40, (1) 24-28.

Hamed, S.A., Abdellah, M.M., & El-Melegy, N. 2004. Blood levels of trace elements, electrolytes, and oxidative stress/antioxidant systems in epileptic patients. *J.Pharmacol.Sci.*, 96, (4) 465-473.

Hamilton, R.M., McKechnie, P.S., & Macfarlane, P.W. 2004. Can cardiac vagal tone be estimated from the 10-second ECG? *International Journal of Cardiology*, 95, (1) 109-115.

Hanley, J.A., Negassa, A., Edwardes, M.D., & Forrester, J.E. 2003. Statistical analysis of correlated data using generalized estimating equations: an orientation. *American Journal of Epidemiology*, 157, (4) 364-375.

Harati, Y. 1993, "Anatomy of the Spinal and Peripheral Autonomic Nervous System," *In Clinical Autonomic Disorders: Evaluation and management.*, 1st ed. P. A. Low, ed., Rochester, Minnesota: Mayo Foundation, pp. 17-38.

Harnod, T., Yang, C.C., Hsin, Y.L., Wang, P.J., Shieh, K.R., & Kuo, T.B. 2009. Heart rate variability in patients with frontal lobe epilepsy. *Seizure.*, 18, (1) 21-25.

Hennessy, M.J., Tighe, M.G., Binnie, C.D., & Nashef, L. 2001. Sudden withdrawal of carbamazepine increases cardiac sympathetic activity in sleep. *Neurology*, 57, (9) 1650-1654.

Hilz, M. J. 2008, "Female and Male Sexual Dysfunction," *In Clinical Autonomic Disorders*, 3rd ed. Phillip A Low & E. E. Bennaroch, eds., Philadelphia: Lippincott Williams&Wilkins, pp. 657-711.

Hilz, M.J., Devinsky, O., Doyle, W., Mauerer, A., & Dutsch, M. 2002. Decrease of sympathetic cardiovascular modulation after temporal lobe epilepsy surgery. *Brain*, 125, (Pt 5) 985-995.

Hirsch, J., Leibel, R.L., Mackintosh, R., & Aguirre, A. 1991. Heart rate variability as a measure of autonomic function during weight change in humans. *Am.J.Physiol*, 261, (6 Pt 2) R1418-R1423.

Hofstra, W.A. & De Weerd, A.W. 2009. The circadian rhythm and its interaction with human epilepsy: A review of literature. *Sleep Med.Rev.*, 14, (4) 617-621.

Hogan, R.E. & Rao, V.K. 2006. Hemifacial motor and crying seizures of temporal lobe onset: case report and review of electro-clinical localisation. *Journal of Neurology, Neurosurgery and Psychiatry*, 77, (1) 107-110.

Holstege, G. & Collewijn H 2008, "Central Nervous System Control of Micturation," *In Clinical Autonomic Disorders*, 3rd ed. Phillip A Low & E. E. Bennaroch, eds., Philadelphia: Lippincott Williams & Wilkins, pp. 74-87.

Howell, S.J. & Blumhardt, L.D. 1989. Cardiac asystole associated with epileptic seizures: a case report with simultaneous EEG and ECG. *Journal of Neurology, Neurosurgery and Psychiatry*, 52, (6) 795-798.

Hunt, B.E., Farquhar, W.B., & Taylor, J.A. 2001. Does reduced vascular stiffening fully explain preserved cardiovagal baroreflex function in older, physically active men? *Circulation*, 103, (20) 2424-2427.

Hurd, R.W., Van Rinsvelt, H.A., Wilder, B.J., Karas, B., Maenhaut, W., & De, R.L. 1984. Selenium, zinc, and copper changes with valproic acid: possible relation to drug side effects. *Neurology*, 34, (10) 1393-1395.

Ide, A. & Kamijo, Y. 2007. Intermittent complete atrioventricular block after long term low-dose carbamazepine therapy with a serum concentration less than the therapeutic level. *Internal Medicine*, 46, (9) 627-629.

Ilhan, A., Uz, E., Kali, S., Var, A., & Akyol, O. 1999. Serum and hair trace element levels in patients with epilepsy and healthy subjects: does the antiepileptic therapy affect the element concentrations of hair? *European Journal of Neurology*, 6, (6) 705-709.

Ives, J.R., Mainwaring, N.R., Krishnamurthy, K.B., Blum, A.S., Drislane, F.W., Schachter, S.C., & Schomer, D.L. 1996. Technical implementation and clinical findings/results of monitoring oxygen saturation in patients referred for long-term EEG monitoring. *Electroencephalography and Clinical Neurophysiology*, 99, (5) 432-439.

Jansen, K. & Lagae, L. 2010. Cardiac changes in epilepsy. *Seizure.*

Janszky, J., Ebner, A., Szupera, Z., Schulz, R., Hollo, A., Szucs, A., & Clemens, B. 2004. Orgasmic aura--a report of seven cases. *Seizure.*, 13, (6) 441-444.

Johnson, C.D., Rivera, H., & Jimenez, J.E. 1997. Carbamazepine-induced sinus node dysfunction. *Puerto Rico Health Sciences Journal*, 16, (1) 45-49.

Jokeit H, Noerpel I, Herbord E, Ebner A. 2000. Heart rate does not decrease after right hemispheric amobarbital injection. *Neurology*, 54, 2347-8.

Jons, C., Raatikainen, P., Gang, U.J., Huikuri, H.V., Joergensen, R.M., Johannesen, A., Dixen, U., Messier, M., McNitt, S., & Thomsen, P.E. 2010. Autonomic Dysfunction and New-Onset Atrial Fibrillation in Patients With Left Ventricular Systolic Dysfunction After Acute Myocardial Infarction: A CARISMA Substudy. *Journal of Cardiovascular Electrophysiology.* May 7 (Epub ahead of print)

Kamath, M.V. & Fallen, E.L. 1993. Power spectral analysis of heart rate variability: a noninvasive signature of cardiac autonomic function. *Crit Rev.Biomed.Eng*, 21, (3) 245-311.

Kapustecki, J., Rosciszewska, D., & Pierzchala, K. 2000. [Secretion of catecholamines in urine of patients with tonic-clonic epileptic seizures]. *Wiadomosci Lekarskie*, 53, (9-10) 499-506.

Kara, T., Narkiewicz, K., & Somers, V.K. 2003. Chemoreflexes--physiology and clinical implications. *Acta Physiol Scand.*, 177, (3) 377-384.

Kardelen, F., Akcurin, G., Ertug, H., Akcurin, S., & Bircan, I. 2006. Heart rate variability and circadian variations in type 1 diabetes mellitus. *Pediatr.Diabetes*, 7, (1) 45-50.

Karp, E., Shiyovich, A., Zahger, D., Gilutz, H., Grosbard, A., & Katz, A. 2009. Ultra-Short-Term Heart Rate Variability for Early Risk Stratification following Acute ST-Elevation Myocardial Infarction. *Cardiology*, 114, (4) 275-283.

Kazemi, N.J., Worrell, G.A., Stead, S.M., Brinkmann, B.H., Mullan, B.P., O'Brien, T.J., & So, E.L. 2010. Ictal SPECT statistical parametric mapping in temporal lobe epilepsy surgery. *Neurology*, 74, (1) 70-76.

Keilson, M.J., Hauser, W.A., & Magrill, J.P. 1989. Electrocardiographic changes during electrographic seizures. *Archives of Neurology*, 46, (11) 1169-1170.

Kenneback, G., Ericson, M., Tomson, T., & Bergfeldt, L. 1997. Changes in arrhythmia profile and heart rate variability during abrupt withdrawal of antiepileptic drugs. Implications for sudden death. *Seizure.*, 6, (5) 369-375.

Kerling, F., Dutsch, M., Linke, R., Kuwert, T., Stefan, H., & Hilz, M.J. 2009. Relation between ictal asystole and cardiac sympathetic dysfunction shown by MIBG-SPECT. *Acta Neurologica Scandinavica*, 120, (2) 123-129.

Khatun, S., Kanayama, N., Hossain, B., el, M.E., Kobayashi, T., Jahan, S., Bhuiyan, A.B., & Terao, T. 1997. Increased concentrations of plasma epinephrine and norepinephrine in patients with eclampsia. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, 74, (1) 103-109.

Kiok, M.C., Terrence, C.F., Fromm, G.H., & Lavine, S. 1986. Sinus arrest in epilepsy. *Neurology*, 36, (1) 115-116.

Kleiger, R.E., Stein, P.K., & Bigger, J.T., Jr. 2005. Heart rate variability: measurement and clinical utility. *Ann.Noninvasive.Electrocardiol.*, 10, (1) 88-101.

Koe, A.S., Jones, N.C., & Salzberg, M.R. 2009. Early Life Stress as an Influence on Limbic Epilepsy: An Hypothesis Whose Time has Come? *Front Behav.Neurosci.*, 3, 24.

Korpelainen, J.T., Sotaniemi, K.A., Huikuri, H.V., & Myllyla, V.V. 1997. Circadian rhythm of heart rate variability is reversibly abolished in ischemic stroke. *Stroke*, 28, (11) 2150-2154.

Kramer, R.E., Luders, H., Goldstick, L.P., Dinner, D.S., Morris, H.H., Lesser, R.P., & Wyllie, E. 1988. Ictus emeticus: an electroclinical analysis. *Neurology*, 38, (7) 1048-1052.

Kuba, R., Pohanka, M., Zakopcan, J., Novotna, I., & Rektor, I. 2006. Sexual dysfunctions and blood hormonal profile in men with focal epilepsy. *Epilepsia*, 47, (12) 2135-2140.

Kumada, T., Hattori, H., Doi, H., Shiraishi, K., Yamanaka, Y., Kato, T., & Nakahata, T. 2005. [Postoperative complete atrioventricular block induced by carbamazepine in a patient with congenital heart disease]. *No to Hattatsu*, 37, (3) 257-261.

Kuo, T.B., Lin, T., Yang, C.C., Li, C.L., Chen, C.F., & Chou, P. 1999. Effect of aging on gender differences in neural control of heart rate. *Am.J.Physiol*, 277, (6 Pt 2) H2233-H2239.

Kurekci, A.E., Alpay, F., Tanindi, S., Gokcay, E., Ozcan, O., Akin, R., Isimer, A., & Sayal, A. 1995. Plasma trace element, plasma glutathione peroxidase, and superoxide dismutase levels in epileptic children receiving antiepileptic drug therapy. *Epilepsia*, 36, (6) 600-604.

Kutlu, G., Bilir, E., Erdem, A., Gomceli, Y.B., Leventoglu, A., Kurt, G.S., Karatas, A., & Serdaroglu, A. 2005. Temporal lobe ictal behavioral patterns in hippocampal sclerosis and other structural abnormalities. *Epilepsy Behav.*, 6, (3) 353-359.

Labrecque, J., Cote, M.A., & Vincent, P. 1992. Carbamazepine-induced atrioventricular block. *American Journal of Psychiatry*, 149, (4) 572-573.

Ladefoged, S.D. & Mogelvang, J.C. 1982. Total atrioventricular block with syncopes complicating carbamazepine therapy. *Acta Medica Scandinavica*, 212, (3) 185-186.

Lamusuo, S., Ruottinen, H.M., Knuuti, J., Harkonen, R., Ruotsalainen, U., Bergman, J., Haaparanta, M., Solin, O., Mervaala, E., Nousiainen, U., Jaaskelainen, S., Ylinen, A., Kalviainen, R., Rinne, J.K., Vapalahti, M., & Rinne, J.O. 1997. Comparison of [18F]FDG-PET, [99mTc]-HMPAO-SPECT, and [123I]-iomazenil-SPECT in localising the epileptogenic cortex. *Journal of Neurology, Neurosurgery and Psychiatry*, 63, (6) 743-748.

Langan, Y. 2000. Sudden unexpected death in epilepsy (SUDEP): risk factors and case control studies. *Seizure.*, 9, (3) 179-183.

Langan, Y., Nashef, L., & Sander, J.W. 2005. Case-control study of SUDEP. *Neurology*, 64, (7) 1131-1133.

Langan, Y., Nolan, N., & Hutchinson, M. 1998. The incidence of sudden unexpected death in epilepsy (SUDEP) in South Dublin and Wicklow. *Seizure.*, 7, (5) 355-358.

Lathers, C.M. & Schraeder, P.L. 1982. Autonomic dysfunction in epilepsy: characterization of autonomic cardiac neural discharge associated with pentylenetetrazol-induced epileptogenic activity. *Epilepsia*, 23, (6) 633-647.

Lathers, C.M. & Schraeder, P.L. 1987. Review of autonomic dysfunction, cardiac arrhythmias, and epileptogenic activity. *Journal of Clinical Pharmacology*, 27, (5) 346-356.

Lee, S., Harris, N.D., Robinson, R.T., Yeoh, L., Macdonald, I.A., & Heller, S.R. 2003. Effects of adrenaline and potassium on QTc interval and QT dispersion in man. *Eur.J.Clin.Invest*, 33, (2) 93-98.

Lee, S.A., Lee, S.M., & No, Y.J. 2009. Factors contributing to depression in patients with epilepsy. *Epilepsia,* 51, (7) 1305-1308.

Leestma, J.E., Walczak, T., Hughes, J.R., Kalelkar, M.B., & Teas, S.S. 1989. A prospective study on sudden unexpected death in epilepsy. *Annals of Neurology*, 26, (2) 195-203.

Legriel, S., Bruneel, F., Dalle, L., Appere-de-Vecchi, C., Georges, J.L., Abbosh, N., Henry-Lagarrigue, M., Revault, D.L., Ben, M.H., Audibert, J., Guezennec, P., Troche, G., & Bedos, J.P. 2008. Recurrent takotsubo cardiomyopathy triggered by convulsive status epilepticus. *Neurocrit.Care*, 9, (1) 118-121.

Leutmezer, F., Schernthaner, C., Lurger, S., Potzelberger, K., & Baumgartner, C. 2003. Electrocardiographic changes at the onset of epileptic seizures. *Epilepsia*, 44, (3) 348-354.

Longin, E., Gerstner, T., Lenz, T., & Konig, S. 2007. 'Influence of subclinical generalized spike-wave activity on the heart rate of children with epilepsy'. *Developmental Medicine and Child Neurology*, 49, (1) 80.

Luef, G.J. 2008. Epilepsy and sexuality. *Seizure.*, 17, (2) 127-130.

Luo, S., Michler, K., Johnston, P., & Macfarlane, P.W. 2004. A comparison of commonly used QT correction formulae: the effect of heart rate on the QTc of normal ECGs. *Journal of Electrocardiology*, 37 Suppl, 81-90.

Malik, M. 1996. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *European Heart Journal*, 17, (3) 354-381.

Malik, M. & Camm, A.J. 1994. Heart rate variability and clinical cardiology. *British Heart Journal*, 71, (1) 3-6.

Malik, M., Farrell, T., & Camm, A.J. 1990. Circadian rhythm of heart rate variability after acute myocardial infarction and its influence on the prognostic value of heart rate variability. *American Journal of Cardiology*, 66, (15) 1049-1054.

Malliani, A., Pagani, M., Lombardi, F., & Cerutti, S. 1991. Cardiovascular neural regulation explored in the frequency domain. *Circulation*, 84, (2) 482-492.

Malpas, S.C. & Purdie, G.L. 1990. Circadian variation of heart rate variability. *Cardiovascular Research*, 24, (3) 210-213.

Mameli, P., Mameli, O., Tolu, E., Padua, G., Giraudi, D., Caria, M.A., & Melis, F. 1988. Neurogenic myocardial arrhythmias in experimental focal epilepsy. *Epilepsia*, 29, (1) 74-82.

Marks, W.J., Jr. & Laxer, K.D. 1998. Semiology of temporal lobe seizures: value in lateralizing the seizure focus. *Epilepsia*, 39, (7) 721-726.

Mascia, A., Quarato, P.P., Sparano, A., Esposito, V., Sebastiano, F., Occhiogrosso, G., & Di, G.G. 2005. Cardiac asystole during right frontal lobe seizures: a case report. *Neurol.Sci.*, 26, (5) 340-343.

Massetani, R., Strata, G., Galli, R., Gori, S., Gneri, C., Limbruno, U., Di, S.D., Mariani, M., & Murri, L. 1997. Alteration of cardiac function in patients with temporal lobe epilepsy: different roles of EEG-ECG monitoring and spectral analysis of RR variability. *Epilepsia*, 38, (3) 363-369.

Mathias, C.J., Deguchi, K., & Schatz, I. 2001. Observations on recurrent syncope and presyncope in 641 patients. *Lancet*, 357, (9253) 348-353.

Mayer, H., Benninger, F., Urak, L., Plattner, B., Geldner, J., & Feucht, M. 2004. EKG abnormalities in children and adolescents with symptomatic temporal lobe epilepsy. *Neurology*, 63, (2) 324-328.

McLachlan, R.S. 2009. A brief review of the anatomy and physiology of the limbic system. *Canadian Journal of Neurological Sciences*, 36 Suppl 2, S84-S87.

Mitchell, W.G., Greenwood, R.S., & Messenheimer, J.A. 1983. Abdominal epilepsy. Cyclic vomiting as the major symptom of simple partial seizures. *Archives of Neurology*, 40, (4) 251-252.

Molleken, D., Richter-Appelt, H., Stodieck, S., & Bengner, T. 2009. Sexual quality of life in epilepsy: correlations with sex hormone blood levels. *Epilepsy Behav.*, 14, (1) 226-231.

Morgan, H. 1990. Dostoevsky's epilepsy: a case report and comparison. *Surgical Neurology*, 33, (6) 413-416.

Morrell, M. J. 2008, "Sexuality in Epilepsy," *In Epilpesy;A Comprehensive Textbook*, 2nd ed. vol. 2 Engel J & Pedley TA, eds., Philadelphia: Wolters Kluwer Lippincott Williams & Wilkins, pp. 2062-2065.

Mosier, J.M., White, P., GRANT, P., Fisher, J.E., & TAYLOR, R. 1957. Cerebroautonomic and myographic changes accompanying induced seizures. *Neurology*, 7, (3) 204-210.

Mukherjee, S., Tripathi, M., Chandra, P.S., Yadav, R., Choudhary, N., Sagar, R., Bhore, R., Pandey, R.M., & Deepak, K.K. 2009. Cardiovascular autonomic functions in well-controlled and intractable partial epilepsies. *Epilepsy Research*, 85, (2-3) 261-269.

Nagai, Y., Goldstein, L.H., Critchley, H.D., & Fenwick, P.B. 2004. Influence of sympathetic autonomic arousal on cortical arousal: implications for a therapeutic behavioural intervention in epilepsy. *Epilepsy Research*, 58, (2-3) 185-193.

Naritoku, D.K., Casebeer, D.J., & Darbin, O. 2003. Effects of seizure repetition on postictal and interictal neurocardiac regulation in the rat. *Epilepsia*, 44, (7) 912-916.

Nashef, L. 1997. Sudden unexpected death in epilepsy: terminology and definitions. *Epilepsia*, 38, (11 Suppl) S6-S8.

Nashef, L. & Shorvon, S.D. 1997. Mortality in epilepsy. *Epilepsia*, 38, (10) 1059-1061.

Nashef, L., Walker, F., Allen, P., Sander, J.W., Shorvon, S.D., & Fish, D.R. 1996. Apnoea and bradycardia during epileptic seizures: relation to sudden death in epilepsy. *Journal of Neurology, Neurosurgery and Psychiatry*, 60, (3) 297-300.

Natelson, B.H., Suarez, R.V., Terrence, C.F., & Turizo, R. 1998. Patients with epilepsy who die suddenly have cardiac disease. *Archives of Neurology*, 55, (6) 857-860.

Natelson, S., Miletich, D.J., Seals, C.F., Visintine, D.J., & Albrecht, R.F. 1979a. Clinical biochemistry of epilepsy. I. Nature of the disease and a review of the chemical findings in epilepsy. *Clinical Chemistry*, 25, (6) 889-897.

Natelson, S., Miletich, D.J., Seals, C.F., Visintine, D.J., & Albrecht, R.F. 1979b. Clinical biochemistry of epilepsy. II. Observations on two types of epileptiform convulsions induced in rabbits with corticotropin. *Clinical Chemistry*, 25, (6) 898-913.

Nei, M. & Hays, R. 2010. Sudden unexpected death in epilepsy. *Curr.Neurol.Neurosci.Rep.*, 10, (4) 319-326.

Nei, M., Ho, R.T., & Sperling, M.R. 2000. EKG abnormalities during partial seizures in refractory epilepsy. *Epilepsia*, 41, (5) 542-548.

Nelissen, N., Van, P.W., Baete, K., Van, L.K., Palmini, A., Van, B.H., & Dupont, P. 2006. Correlations of interictal FDG-PET metabolism and ictal SPECT perfusion changes in human temporal lobe epilepsy with hippocampal sclerosis. *Neuroimage.*, 32, (2) 684-695.

Neufeld, G., Lazar, J.M., Chari, G., Kamran, H., Akajagbor, E., Salciccioli, L., Kassotis, J., & Stewart, M. 2009. Cardiac repolarization indices in epilepsy patients. *Cardiology*, 114, (4) 255-260.

Nieminen, T. & Verrier, R.L. 2010. Usefulness of T-wave alternans in sudden death risk stratification and guiding medical therapy. *Ann.Noninvasive.Electrocardiol.*, 15, (3) 276-288.

Nilsson, L., Farahmand, B.Y., Persson, P.G., Thiblin, I., & Tomson, T. 1999. Risk factors for sudden unexpected death in epilepsy: a case-control study. *Lancet*, 353, (9156) 888-893.

Novy, J., Carruzzo, A., Pascale, P., Maeder-Ingvar, M., Genne, D., Pruvot, E., Despland, P.A., & Rossetti, A.O. 2009. Ictal bradycardia and asystole: an uncommon cause of syncope. *International Journal of Cardiology*, 133, (3) e90-e93.

Nzeh, D.A., Erasmus, R.T., & Aiyedun, B.A. 1994. Serum electrolyte and protein changes after intravenous injection of sodium and meglumine diatrizoate (urograffin-370). *African Journal of Medicine and Medical Sciences*, 23, (1) 35-37.

O'Donovan, C.A., Burgess RC, & Luders, H.O. 1995. Computerised seizure detection based on heart rate changes. *Epilepsia*, 36, (S4) 7.

O'Regan, M.E. & Brown, J.K. 2005. Abnormalities in cardiac and respiratory function observed during seizures in childhood. *Developmental Medicine and Child Neurology*, 47, (1) 4-9.

Opeskin, K. & Berkovic, S.F. 2003. Risk factors for sudden unexpected death in epilepsy: a controlled prospective study based on coroners cases. *Seizure.*, 12, (7) 456-464.

Opeskin, K., Harvey, A.S., Cordner, S.M., & Berkovic, S.F. 2000. Sudden unexpected death in epilepsy in Victoria. *J.Clin.Neurosci.*, 7, (1) 34-37.

Opherk, C., Coromilas, J., & Hirsch, L.J. 2002a. Heart rate and EKG changes in 102 seizures: analysis of influencing factors. *Epilepsy Research*, 52, (2) 117-127.

Opherk, C. & Hirsch, L.J. 2002b. Ictal heart rate differentiates epileptic from non-epileptic seizures. *Neurology*, 58, (4) 636-638.

Oppenheimer, S. 1993. The anatomy and physiology of cortical mechanisms of cardiac control. *Stroke*, 24, (12 Suppl) I3-I5.

Oppenheimer, S. 2006. Cerebrogenic cardiac arrhythmias: cortical lateralization and clinical significance. *Clinical Autonomic Research*, 16, (1) 6-11.

Oppenheimer, S. 2007. Cortical control of the heart. *Cleveland Clinic Journal of Medicine*, 74 Suppl 1, S27-S29.

Oppenheimer, S.M. & Cechetto, D.F. 1990. Cardiac chronotropic organization of the rat insular cortex. *Brain Research*, 533, (1) 66-72.

Oppenheimer, S.M., Gelb, A., Girvin, J.P., & Hachinski, V.C. 1992. Cardiovascular effects of human insular cortex stimulation. *Neurology*, 42, (9) 1727-1732.

Oppenheimer, S.M., Kedem, G., & Martin, W.M. 1996. Left-insular cortex lesions perturb cardiac autonomic tone in humans. *Clinical Autonomic Research*, 6, (3) 131-140.

Otaigbe, B.E. 2008. Infantile masturbation in an African female: is this a justification for female genital cutting? *World J.Pediatr.*, 4, (2) 148-151.

Panayiotopoulos, C. P. 2007, "Epileptic Seizures and Their Classification," *In A Clinical Guide to Epileptic Syndrome and Their Treatment*, 2nd ed. London: Springer-Verlag, pp. 17-56.

Parihar, P.S., Thussu, A., Sharma, S., & Prabhakar, S. 1996. Carbamazepine induced sino-atrial block in a young adult. *Journal of the Association of Physicians of India*, 44, (6) 431-432.

Penfield, W.P. & Rasmussen T 1957. *The Cerebral Cortex of Man: A Clinical Study of Localization of Function* New York, Macmillan.

Persson, H., Ericson, M., & Tomson, T. 2003. Carbamazepine affects autonomic cardiac control in patients with newly diagnosed epilepsy. *Epilepsy Research*, 57, (1) 69-75.

Persson, H., Ericson, M., & Tomson, T. 2007a. Heart rate variability in patients with untreated epilepsy. *Seizure.*, 16, (6) 504-508.

Persson, H., Kumlien, E., Ericson, M., & Tomson, T. 2007b. Circadian variation in heart-rate variability in localization-related epilepsy. *Epilepsia*, 48, (5) 917-922.

Ponikowski, P., Rosano, G.M., Amadi, A.A., Collins, P., Coats, A.J., Poole-Wilson, P.A., & Kaski, J.C. 1996. Transient autonomic dysfunction precedes ST-segment depression in patients with syndrome X. *American Journal of Cardiology*, 77, (11) 942-947.

Pritchard, P.B., III, Wannamaker, B.B., Sagel, J., Nair, R., & DeVillier, C. 1983. Endocrine function following complex partial seizures. *Annals of Neurology*, 14, (1) 27-32.

Quattrone, A., Crunelli, V., & Samanin, R. 1978. Seizure susceptibility and anticonvulsant activity of carbamazepine, diphenylhydantoin and phenobarbital in rats with selective depletions of brain monoamines. *Neuropharmacology*, 17, (8) 643-647.

Radhakrishnan, K., So, E.L., Silbert, P.L., Jack, C.R., Jr., Cascino, G.D., Sharbrough, F.W., & O'Brien, P.C. 1998. Predictors of outcome of anterior temporal lobectomy for intractable epilepsy: a multivariate study. *Neurology*, 51, (2) 465-471.

Reis, D.J. & Oliphant, M.C. 1964. Bradycardia and tachycardia following electrical stimulation of the amygdaloid region in monkey. *Journal of Neurophysiology*, 27, 893-912.

Reynolds, E.H. 1970. Water, electrolytes and epilepsy. *Journal of the Neurological Sciences*, 11, (4) 327-358.

Riediker, M., Herbst, M.C., Devlin, R.B., Griggs, T.R., Bromberg, P.A., & Cascio, W.E. 2005. Effect of the September 11, 2001 terrorist attack on a state highway patrol trooper's heart rate variability. *Ann.Noninvasive.Electrocardiol.*, 10, (1) 83-85.

Ronkainen, E., Ansakorpi, H., Huikuri, H.V., Myllyla, V.V., Isojarvi, J.I., & Korpelainen, J.T. 2005. Suppressed circadian heart rate dynamics in temporal lobe epilepsy. *Journal of Neurology, Neurosurgery and Psychiatry*, 76, (10) 1382-1386.

Rosenzweig, I. & Manford, M. 2008. Trouble at dinner: an unusual case of eating-induced seizures. *Journal of Neurology, Neurosurgery and Psychiatry*, 79, (3) 335-337.

Rugg-Gunn, F.J., Duncan, J.S., & Smith, S.J. 2000. Epileptic cardiac asystole. *Journal of Neurology, Neurosurgery and Psychiatry*, 68, (1) 108-110.

Rutecki, P. 1990. Anatomical, physiological, and theoretical basis for the antiepileptic effect of vagus nerve stimulation. *Epilepsia*, 31 Suppl 2, S1-S6.

Sakamoto, K., Saito, T., Orman, R., Koizumi, K., Lazar, J., Salciccioli, L., & Stewart, M. 2008. Autonomic consequences of kainic acid-induced limbic cortical seizures in rats: peripheral autonomic nerve activity, acute cardiovascular changes, and death. *Epilepsia*, 49, (6) 982-996.

Salahuddin, L., Cho, J., Jeong, M.G., & Kim, D. 2007. Ultra short term analysis of heart rate variability for monitoring mental stress in mobile settings. *Conf.Proc.IEEE Eng Med.Biol.Soc.*, 2007, 4656-4659.

Sander, J. W. 2007, "The Incidence and prevalence of Epilepsy," *In EPILEPSY 2007 FROM CELL TO COMMUNITY LECTURE NOTES for the Eleventh Epilepsy Teaching Weekend 28-30 September 2007 St Anne's College, Oxford*, 11th ed. J. W. Sander, alker M C, & J. E. Malls, eds., London: Interantional League Against Epilepsy(UK Chapter) and National Society for Epilepsy, pp. 1-3.

Sander, J.W. & Shorvon, S.D. 1996. Epidemiology of the epilepsies. *Journal of Neurology, Neurosurgery and Psychiatry*, 61, (5) 433-443.

Sapoznikov, D., Luria, M.H., Mahler, Y., & Gotsman, M.S. 1992. Day vs night ECG and heart rate variability patterns in patients without obvious heart disease. *Journal of Electrocardiology*, 25, (3) 175-184.

Sathyaprabha, T.N., Satishchandra, P., Netravathi, K., Sinha, S., Thennarasu, K., & Raju, T.R. 2006. Cardiac autonomic dysfunctions in chronic refractory epilepsy. *Epilepsy Research*, 72, (1) 49-56.

Schachter, S. C. 2009, "Vagal Nerve stimulation," *In The Treatment of Epilepsy*, 3rd ed. Simon Shorvon, Emilio Perucca, & Jerome Engel Jr, eds., Singapore: Blackwell Publishing Ltd, pp. 1017-1023.

Schank, J.R., Liles, L.C., & Weinshenker, D. 2005. Reduced anticonvulsant efficacy of valproic acid in dopamine beta-hydroxylase knockout mice. *Epilepsy Research*, 65, (1-2) 23-31.

Schernthaner, C., Lindinger, G., Potzelberger, K., Zeiler, K., & Baumgartner, C. 1999. Autonomic epilepsy--the influence of epileptic discharges on heart rate and rhythm. *Wiener Klinische Wochenschrift*, 111, (10) 392-401.

Schofl, C., Becker, C., Prank, K., von zur, M.A., & Brabant, G. 1997. Twenty-four-hour rhythms of plasma catecholamines and their relation to cardiovascular parameters in healthy young men. *European Journal of Endocrinology / European Federation of Endocrine Societies*, 137, (6) 675-683.

Schuele, S.U., Bermeo, A.C., Alexopoulos, A.V., Locatelli, E.R., Burgess, R.C., Dinner, D.S., & Foldvary-Schaefer, N. 2007. Video-electrographic and clinical features in patients with ictal asystole. *Neurology*, 69, (5) 434-441.

Schuele, S.U., Bermeo, A.C., Locatelli, E., Burgess, R.C., & Luders, H.O. 2008. Ictal asystole: a benign condition? *Epilepsia*, 49, (1) 168-171.

Seyal, M. & Bateman, L.M. 2009. Ictal apnea linked to contralateral spread of temporal lobe seizures: Intracranial EEG recordings in refractory temporal lobe epilepsy. *Epilepsia*, 50, (12) 2557-2562.

Shimizu, M., Kagawa, A., Takano, T., Masai, H., & Miwa, Y. 2008. Neurogenic stunned myocardium associated with status epileptics and postictal catecholamine surge. *Internal Medicine*, 47, (4) 269-273.

Simon, R.P., Aminoff, M.J., & Benowitz, N.L. 1984. Changes in plasma catecholamines after tonic-clonic seizures. *Neurology*, 34, (2) 255-257.

Sinclair, D.B. & Unwala, H. 2007. Absence epilepsy in childhood: electroencephalography (EEG) does not predict outcome. *Journal of Child Neurology*, 22, (7) 799-802.

Sinert, R., Zehtabchi, S., Desai, S., Peacock, P., Altura, B.T., & Altura, B.M. 2007. Serum ionized magnesium and calcium levels in adult patients with seizures. *Scand.J.Clin.Lab Invest*, 67, (3) 317-326.

Singh, R.B., Cornelissen, G., Weydahl, A., Schwartzkopff, O., Katinas, G., Otsuka, K., Watanabe, Y., Yano, S., Mori, H., Ichimaru, Y., Mitsutake, G., Pella, D., Fanghong, L., Zhao, Z., Rao, R.S., Gvozdjakova, A., & Halberg, F. 2003. Circadian heart rate and blood pressure variability considered for research and patient care. *International Journal of Cardiology*, 87, (1) 9-28.

Siniscalchi, A., Gallelli, L., Mercuri, N.B., & De, S.G. 2008. Serum prolactin levels in repetitive temporal epileptic seizures. *European Review for Medical and Pharmacological Sciences*, 12, (6) 365-368.

Smilde, T.D., van Veldhuisen, D.J., & van den Berg, M.P. 2009. Prognostic value of heart rate variability and ventricular arrhythmias during 13-year follow-up in patients with mild to moderate heart failure. *Clin.Res.Cardiol.*, 98, (4) 233-239.

Smith, W.G. & Bone, I. 1982. Copper, zinc and magnesium plasma levels in epilepsy. *Journal of Neurology, Neurosurgery and Psychiatry*, 45, (11) 1072.

So, N.K. & Sperling, M.R. 2007. Ictal asystole and SUDEP. *Neurology*, 69, (5) 423-424.

Sohaib, S.M., Papacosta, O., Morris, R.W., Macfarlane, P.W., & Whincup, P.H. 2008. Length of the QT interval: determinants and prognostic implications in a population-based prospective study of older men. *Journal of Electrocardiology*, 41, (6) 704-710.

Standridge, S.M., Holland, K.D., & Horn, P.S. 2010. Cardiac arrhythmias and ictal events within an epilepsy monitoring unit. *Pediatric Neurology*, 42, (3) 201-205.

Strzelczyk, A., Bauer, S., Knake, S., Oertel, W.H., Hamer, H.M., & Rosenow, F. 2008. Ictal asystole in temporal lobe epilepsy before and after pacemaker implantation. *Epileptic Disorders*, 10, (1) 39-44.

Surges, R., Adjei, P., Kallis, C., Erhuero, J., Scott, C.A., Bell, G.S., Sander, J.W., & Walker, M.C. 2010a. Pathologic cardiac repolarization in pharmacoresistant epilepsy and its potential role in sudden unexpected death in epilepsy: A case-control study. *Epilepsia,* 51, (2) 233-242.

Surges, R., Henneberger, C., Adjei, P., Scott, C.A., Sander, J.W., & Walker, M.C. 2009a. Do alterations in inter-ictal heart rate variability predict sudden unexpected death in epilepsy? *Epilepsy Research,* 87, (2-3) 277-286.

Surges, R., Scott, C.A., & Walker, M.C. 2009b. Peri-ictal atrioventricular conduction block in a patient with a lesion in the left insula: case report and review of the literature. *Epilepsy Behav.*, 16, (2) 347-349.

Surges, R., Scott, C.A., & Walker, M.C. 2010b. Enhanced QT shortening and persistent tachycardia after generalized seizures. *Neurology*, 74, (5) 421-426.

Surges, R., Thijs, R.D., Tan, H.L., & Sander, J.W. 2009c. Sudden unexpected death in epilepsy: risk factors and potential pathomechanisms. *Nat.Rev.Neurol.*, 5, (9) 492-504.

Swartz, C.M., Abrams, R., Lane, R.D., DuBois, M.A., & Srinivasaraghavan, J. 1994. Heart rate differences between right and left unilateral electroconvulsive therapy. *Journal of Neurology, Neurosurgery and Psychiatry*, 57, (1) 97-99.

Sztajzel, J., Jung, M., & Bayes de, L.A. 2008. Reproducibility and gender-related differences of heart rate variability during all-day activity in young men and women. *Ann.Noninvasive.Electrocardiol.*, 13, (3) 270-277.

Takayanagi, K., Hisauchi, I., Watanabe, J., Maekawa, Y., Fujito, T., Sakai, Y., Hoshi, K., Kase, M., Nishimura, N., Inoue, T., Hayashi, T., & Morooka, S. 1998. Carbamazepine-induced sinus node dysfunction and atrioventricular block in elderly women. *Japanese Heart Journal*, 39, (4) 469-479.

Talman, W.T. & Kelkar, P. 1993. Neural control of the heart. Central and peripheral. *Neurologic Clinics*, 11, (2) 239-256.

Ten Harkel, A.D., Van Lieshout, J.J., Van Lieshout, E.J., & Wieling, W. 1990. Assessment of cardiovascular reflexes: influence of posture and period of preceding rest. *J.Appl.Physiol*, 68, (1) 147-153.

Thom, M., Seetah, S., Sisodiya, S., Koepp, M., & Scaravilli, F. 2003. Sudden and unexpected death in epilepsy (SUDEP): evidence of acute neuronal injury using HSP-70 and c-Jun immunohistochemistry. *Neuropathology and Applied Neurobiology*, 29, (2) 132-143.

Tigaran, S., Molgaard, H., & Dam, M. 2002. Atrio-ventricular block: a possible explanation of sudden unexpected death in epilepsy. *Acta Neurologica Scandinavica*, 106, (4) 229-233.

Tigaran, S., Molgaard, H., McClelland, R., Dam, M., & Jaffe, A.S. 2003. Evidence of cardiac ischemia during seizures in drug refractory epilepsy patients. *Neurology*, 60, (3) 492-495.

Timmings, P.L. 1998. Sudden unexpected death in epilepsy: is carbamazepine implicated? *Seizure.*, 7, (4) 289-291.

Tinuper, P., Bisulli, F., Cerullo, A., Carcangiu, R., Marini, C., Pierangeli, G., & Cortelli, P. 2001. Ictal bradycardia in partial epileptic seizures: Autonomic investigation in three cases and literature review. *Brain*, 124, (Pt 12) 2361-2371.

Toichi, M., Murai, T., Sengoku, A., & Miyoshi, K. 1998. Interictal change in cardiac autonomic function associated with EEG abnormalities and clinical symptoms: a longitudinal study following acute deterioration in two patients with temporal lobe epilepsy. *Psychiatry and Clinical Neurosciences*, 52, (5) 499-505.

Tomson, T., Ericson, M., Ihrman, C., & Lindblad, L.E. 1998. Heart rate variability in patients with epilepsy. *Epilepsy Research*, 30, (1) 77-83.

Tomson, T., Nashef, L., & Ryvlin, P. 2008. Sudden unexpected death in epilepsy: current knowledge and future directions. *Lancet Neurol.*, 7, (11) 1021-1031.

Toth, V., Hejjel, L., Fogarasi, A., Gyimesi, C., Orsi, G., Szucs, A., Kovacs, N., Komoly, S., Ebner, A., & Janszky, J. 2010. Periictal heart rate variability analysis suggests long-term postictal autonomic disturbance in epilepsy. *European Journal of Neurology*, 17, (6) 780-787.

Ueshima, K., Tachibana, H., Suzuki, T., & Hiramori, K. 2004. Factors affecting the blood concentration of ionized magnesium in patients in the acute phase of myocardial infarction. *Heart and Vessels*, 19, (6) 267-270.

Uluc, K., Saygi, S., Yilmaz, A., & Nurlu, G. 2004. Paroxysmal autonomic alterations mimicking epilepsy: a case report. *Epileptic Disorders*, 6, (2) 125-128.

Vallejo, M., Marquez, M.F., Borja-Aburto, V.H., Cardenas, M., & Hermosillo, A.G. 2005. Age, body mass index, and menstrual cycle influence young women's heart rate variability --a multivariable analysis. *Clinical Autonomic Research*, 15, (4) 292-298.

Van Buren, J.M. 1958. Some autonomic concomitants of ictal automatism; a study of temporal lobe attacks. *Brain*, 81, (4) 505-528.

Van Buren, J.M. 1961. Sensory, motor and autonomic effects of mesial temporal stimulation in man. *Journal of Neurosurgery*, 18, 273-288.

Van Buren, J.M. & Ajmone-Marson, C. 1960. A correlation of autonomic and EEG components in temporal lobe epilepsy. *Archives of Neurology*, 3, 683-703.

Van Buren, J.M., Bucknam, C.A., & Pritchard, W.L. 1961. Autonomic representation in the human orbitotemporal cortex. *Neurology*, 11, 214-224.

Verrier, R.L. & Antzelevitch, C. 2004. Autonomic aspects of arrhythmogenesis: the enduring and the new. *Current Opinion in Cardiology*, 19, (1) 2-11.

Verrotti, A., Laus, M., Coppola, G., Parisi, P., Mohn, A., & Chiarelli, F. 2010. Catamenial epilepsy: hormonal aspects. *Gynecological Endocrinology*, 26, (11) 783-790.

Walczak, T.S., Leppik, I.E., D'Amelio, M., Rarick, J., So, E., Ahman, P., Ruggles, K., Cascino, G.D., Annegers, J.F., & Hauser, W.A. 2001. Incidence and risk factors in sudden unexpected death in epilepsy: a prospective cohort study. *Neurology*, 56, (4) 519-525.

Waller, S.B. & Buterbaugh, G.G. 1985. Convulsive thresholds and severity and the anticonvulsant effect of phenobarbital and phenytoin in adult rats administered 6-hydroxydopamine or 5,7-dihydroxytryptamine during postnatal development. *Pharmacology, Biochemistry and Behavior*, 23, (3) 473-478.

Wannamaker, B.B. 1985. Autonomic nervous system and epilepsy. *Epilepsia*, 26 Suppl 1, S31-S39.

Weil, S., Arnold, S., Eisensehr, I., & Noachtar, S. 2005. Heart rate increase in otherwise subclinical seizures is different in temporal versus extratemporal seizure onset: support for temporal lobe autonomic influence. *Epileptic Disorders*, 7, (3) 199-204.

Weinshenker, D. 2008. The contribution of norepinephrine and orexigenic neuropeptides to the anticonvulsant effect of the ketogenic diet. *Epilepsia*, 49 Suppl 8, 104-107.

White, H.S., Chow, S.Y., Yen-Chow, Y.C., & Woodbury, D.M. 1992. Effect of elevated potassium on the ion content of mouse astrocytes and neurons. *Can.J.Physiol Pharmacol.*, 70 Suppl, S263-S268.

Whitted, A.D., Stanifer, J.W., Dube, P., Borkowski, B.J., Yusuf, J., Komolafe, B.O., Davis, R.C., Jr., Soberman, J.E., & Weber, K.T. 2010. A dyshomeostasis of electrolytes and trace

elements in acute stressor states: impact on the heart. *American Journal of the Medical Sciences*, 340, (1) 48-53.

Wong, C.H., Bleasel, A., Wen, L., Eberl, S., Byth, K., Fulham, M., Somerville, E., & Mohamed, A. 2010. The topography and significance of extratemporal hypometabolism in refractory mesial temporal lobe epilepsy examined by FDG-PET. *Epilepsia,* 51, (8) 1365-1373.

Woodruff, B.K., Britton, J.W., Tigaran, S., Cascino, G.D., Burritt, M.F., McConnell, J.P., Ravkilde, J., Molgaard, H., Andreasen, F., Dam, M., & Jaffe, A.S. 2003. Cardiac troponin levels following monitored epileptic seizures. *Neurology*, 60, (10) 1690-1692.

Wulff, C.H., Ostergaard, J.R., & Storm, K. 1992. Epileptic fits or infantile masturbation? *Seizure.*, 1, (3) 199-201.

Yamamoto, H., Murakami, H., Kamiyama, N., Miyamoto, Y., & Fukuda, M. 2007. A peculiar form of epilepsy induced by crying in infancy. *Brain and Development*, 29, (8) 468-472.

Yamasaki, Y., Kodama, M., Matsuhisa, M., Kishimoto, M., Ozaki, H., Tani, A., Ueda, N., Ishida, Y., & Kamada, T. 1996. Diurnal heart rate variability in healthy subjects: effects of aging and sex difference. *Am.J.Physiol*, 271, (1 Pt 2) H303-H310.

Zamrini, E.Y., Meador, K.J., Loring, D.W., Nichols, F.T., Lee, G.P., Figueroa, R.E., & Thompson, W.O. 1990. Unilateral cerebral inactivation produces differential left/right heart rate responses. *Neurology*, 40, (9) 1408-1411.

Zangaladze, A., Nei, M., Liporace, J.D., & Sperling, M.R. 2008. Characteristics and clinical significance of subclinical seizures. *Epilepsia*, 49, (12) 2016-2021.

Zelena, V., Kuba, R., Pohanka, M., Soska, V., & Rektor, I. 2007. Sexual functions in women with focal epilepsy. A preliminary study. *Epileptic Disorders*, 9 Suppl 1, S83-S92.

Zhang, Z. & Oppenheimer, S.M. 2000a. Electrophysiological evidence for reciprocal insulo-insular connectivity of baroreceptor-related neurons. *Brain Research*, 863, (1-2) 25-41.

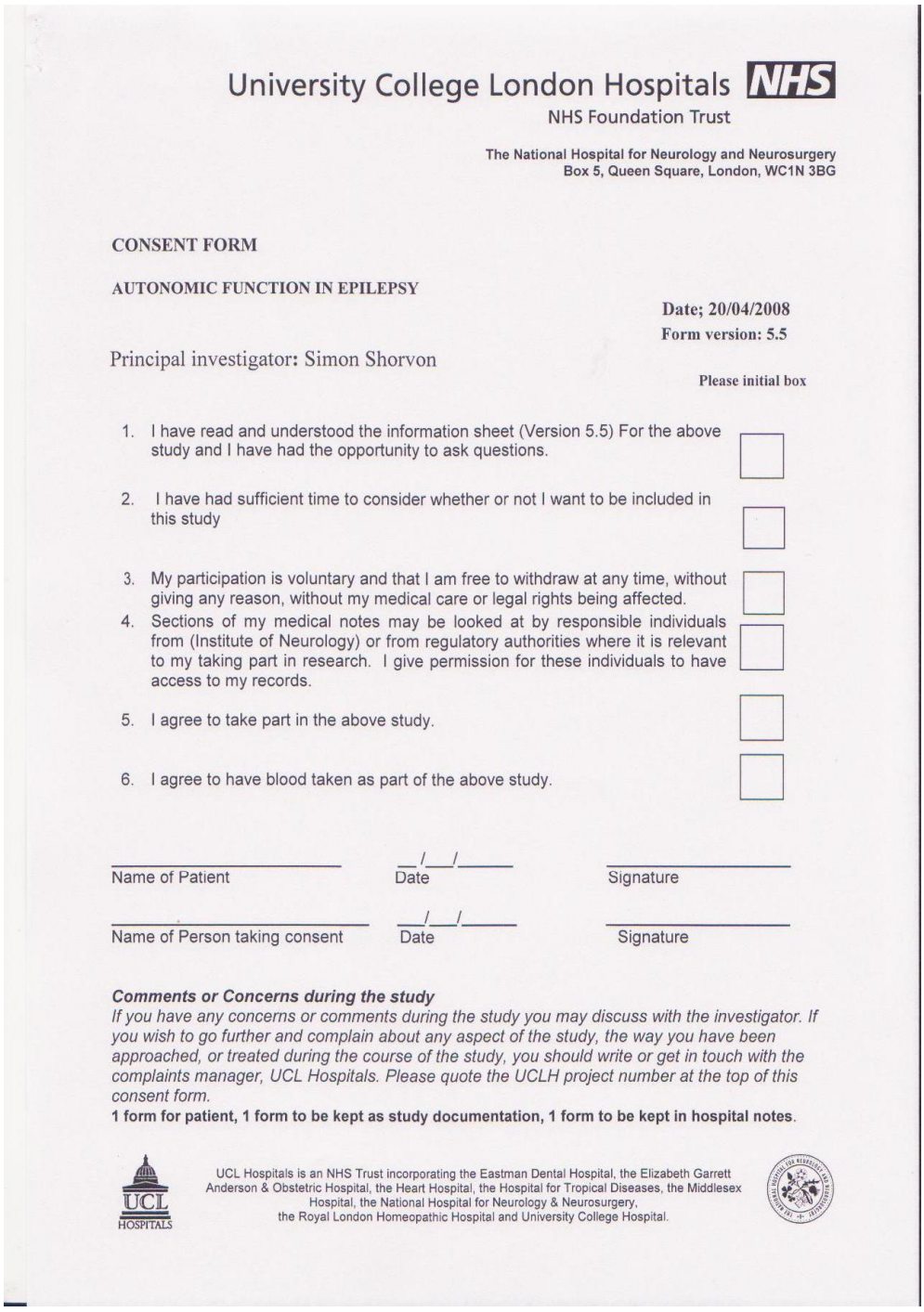
Zhang, Z.H. & Oppenheimer, S.M. 2000b. Baroreceptive and somatosensory convergent thalamic neurons project to the posterior insular cortex in the rat. *Brain Research*, 861, (2) 241-256.

Zijlmans, M., Flanagan, D., & Gotman, J. 2002. Heart rate changes and ECG abnormalities during epileptic seizures: prevalence and definition of an objective clinical sign. *Epilepsia*, 43, (8) 847-854.

Appendices

Appendix 1.1

Copy of Consent form



University College London Hospitals NHS
NHS Foundation Trust

The National Hospital for Neurology and Neurosurgery
Box 5, Queen Square, London, WC1N 3BG

CONSENT FORM

AUTONOMIC FUNCTION IN EPILEPSY

Date; 20/04/2008
Form version: 5.5

Principal investigator: Simon Shorvon

Please initial box

1. I have read and understood the information sheet (Version 5.5) For the above study and I have had the opportunity to ask questions. ☐
2. I have had sufficient time to consider whether or not I want to be included in this study ☐
3. My participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
4. Sections of my medical notes may be looked at by responsible individuals from (Institute of Neurology) or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
5. I agree to take part in the above study. ☐
6. I agree to have blood taken as part of the above study. ☐

Name of Patient	__/___/_____ Date	Signature
Name of Person taking consent	___/___/_____ Date	Signature

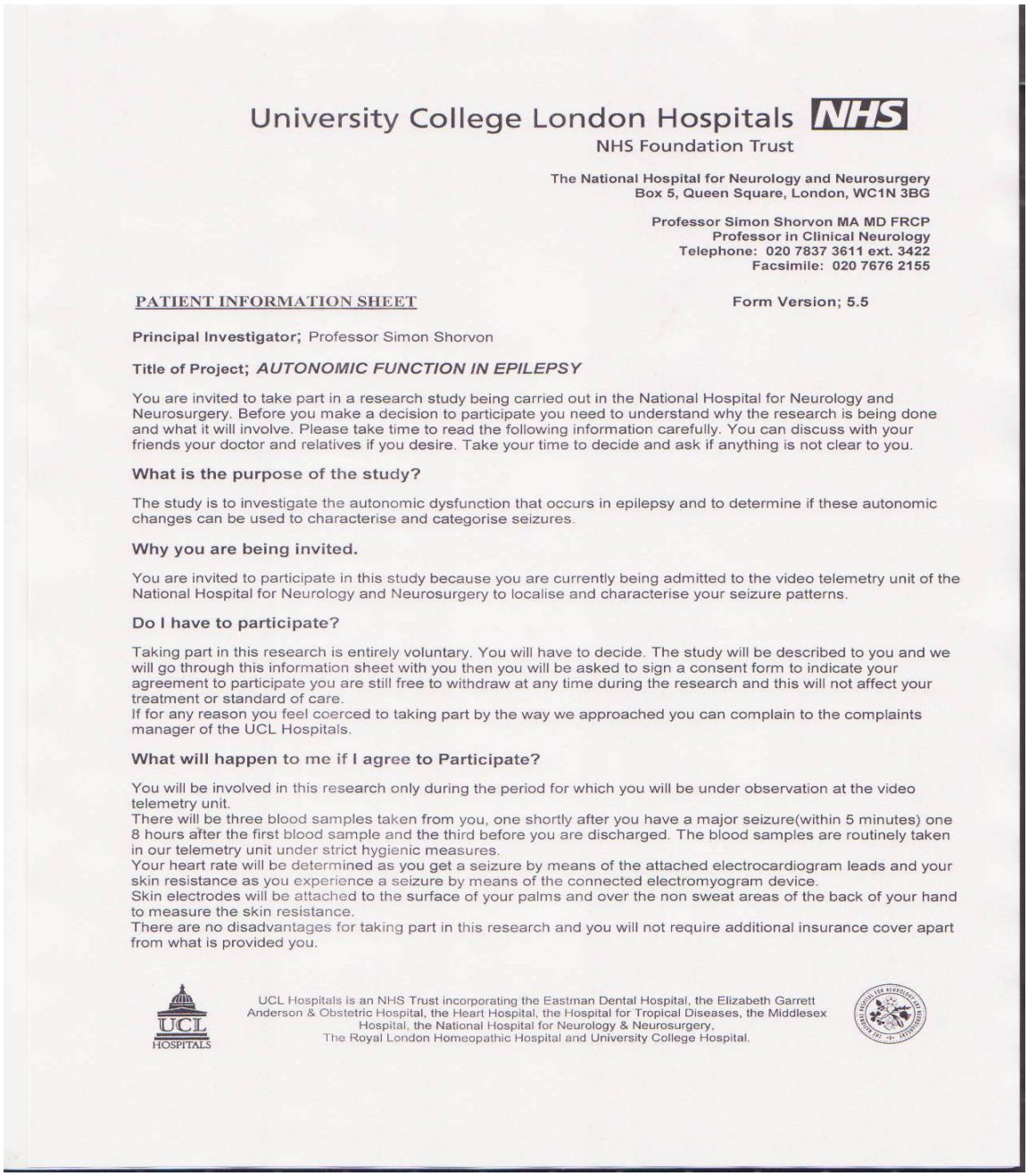
Comments or Concerns during the study
If you have any concerns or comments during the study you may discuss with the investigator. If you wish to go further and complain about any aspect of the study, the way you have been approached, or treated during the course of the study, you should write or get in touch with the complaints manager, UCL Hospitals. Please quote the UCLH project number at the top of this consent form.
1 form for patient, 1 form to be kept as study documentation, 1 form to be kept in hospital notes.

UCL HOSPITALS

UCL Hospitals is an NHS Trust incorporating the Eastman Dental Hospital, the Elizabeth Garrett Anderson & Obstetric Hospital, the Heart Hospital, the Hospital for Tropical Diseases, the Middlesex Hospital, the National Hospital for Neurology & Neurosurgery, the Royal London Homeopathic Hospital and University College Hospital.

Appendix 1.2

Copy of Patient information sheet



University College London Hospitals NHS
NHS Foundation Trust

The National Hospital for Neurology and Neurosurgery
Box 5, Queen Square, London, WC1N 3BG

Professor Simon Shorvon MA MD FRCP
Professor in Clinical Neurology
Telephone: 020 7837 3611 ext. 3422
Facsimile: 020 7676 2155

PATIENT INFORMATION SHEET

Form Version; 5.5

Principal Investigator; Professor Simon Shorvon

Title of Project; ***AUTONOMIC FUNCTION IN EPILEPSY***

You are invited to take part in a research study being carried out in the National Hospital for Neurology and Neurosurgery. Before you make a decision to participate you need to understand why the research is being done and what it will involve. Please take time to read the following information carefully. You can discuss with your friends your doctor and relatives if you desire. Take your time to decide and ask if anything is not clear to you.

What is the purpose of the study?

The study is to investigate the autonomic dysfunction that occurs in epilepsy and to determine if these autonomic changes can be used to characterise and categorise seizures.

Why you are being invited.

You are invited to participate in this study because you are currently being admitted to the video telemetry unit of the National Hospital for Neurology and Neurosurgery to localise and characterise your seizure patterns.

Do I have to participate?

Taking part in this research is entirely voluntary. You will have to decide. The study will be described to you and we will go through this information sheet with you then you will be asked to sign a consent form to indicate your agreement to participate you are still free to withdraw at any time during the research and this will not affect your treatment or standard of care.
If for any reason you feel coerced to taking part by the way we approached you can complain to the complaints manager of the UCL Hospitals.

What will happen to me if I agree to Participate?

You will be involved in this research only during the period for which you will be under observation at the video telemetry unit.
There will be three blood samples taken from you, one shortly after you have a major seizure(within 5 minutes) one 8 hours after the first blood sample and the third before you are discharged. The blood samples are routinely taken in our telemetry unit under strict hygienic measures.
Your heart rate will be determined as you get a seizure by means of the attached electrocardiogram leads and your skin resistance as you experience a seizure by means of the connected electromyogram device.
Skin electrodes will be attached to the surface of your palms and over the non sweat areas of the back of your hand to measure the skin resistance.
There are no disadvantages for taking part in this research and you will not require additional insurance cover apart from what is provided you.

Patient information sheet used for the recruitment; this provided a brief information on the project

There is small chance that a significant abnormality in your ECG and your blood samples may be found that neither you nor the investigator is aware of, in such circumstances you will be referred to the appropriate specialist in consultation with your General practitioner if that is what you will like

What are the benefits of taking part?

The research will not be of benefit to you directly but the information gathered will help improve our understanding and probably the management of epilepsy.

Is my participation confidential?

Yes, we will keep participation confidential under the best legal and ethical practise. Data from this research will be coded to prevent your identity from being revealed. The information will be on a password enabled computer only accessible by Professors Shorvon and Walker and the research fellow. You will not be cited in any publication or report of this research unless you so wish.

What happens if I do not want to continue after I have agreed to participate?

You may ask for any information obtained on you to be destroyed at any time. All information will be treated as strictly confidential.

Who reviewed the study?

All research in the NHS establishment is reviewed by an independent group of people called the research Ethics Committee and this research has been reviewed by the National Hospital for Neurology and Neurosurgery and Institute of Neurology Research Ethics Committee.

What if I want further information regarding the study?

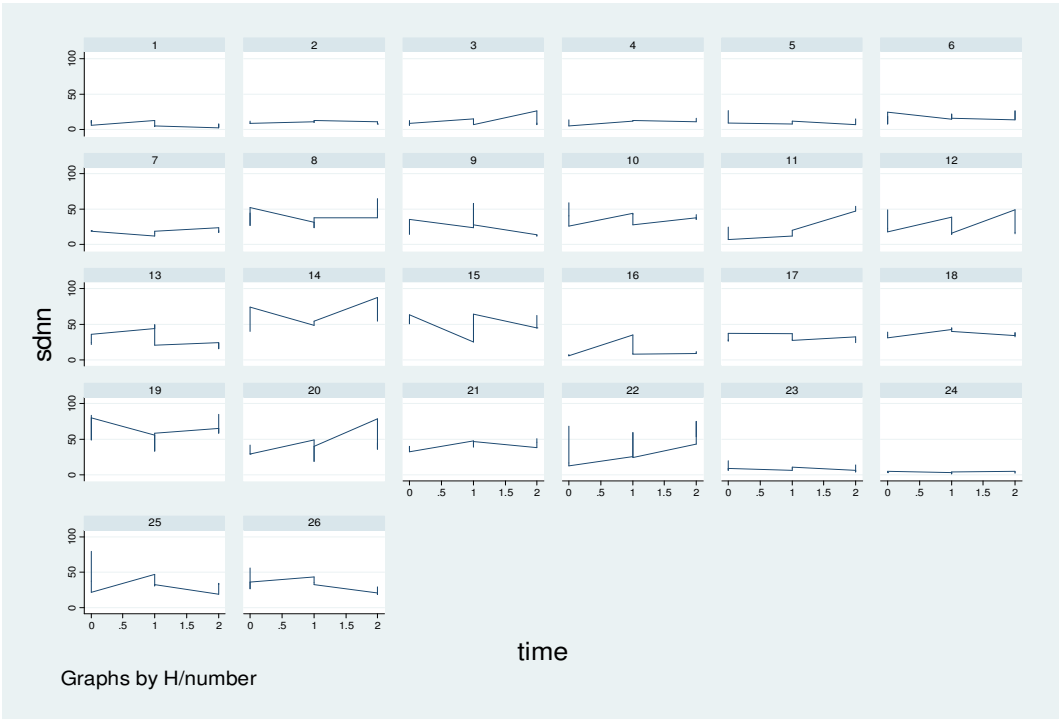
If you have any further questions, please get in touch with Professor Simon Shorvon or Professor Mathew Walker at the Institute of Neurology/National hospital for Neurology and Neurosurgery Queen square, London, WC1N 3BG.Telephone 0207 837 3611ext 3422, Fax; 0207 676 2155.

Thank you for you cooperation.

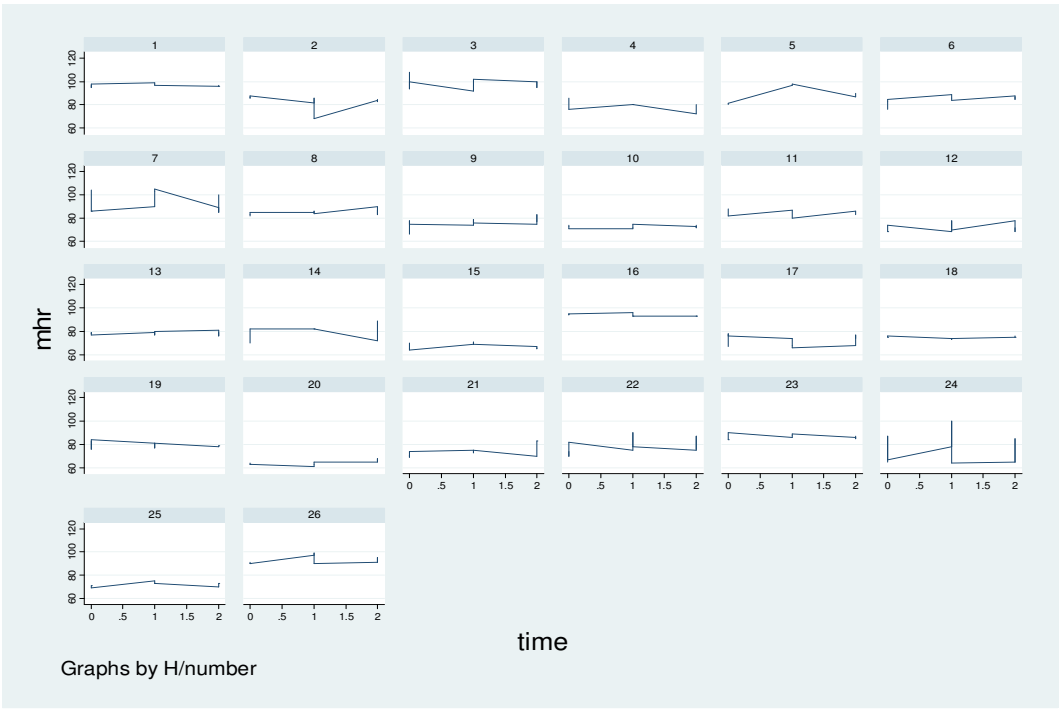
Patient information sheet continued.

Appendix 1.3

Individual HRV plots during subclincal seizures (chapter 4)

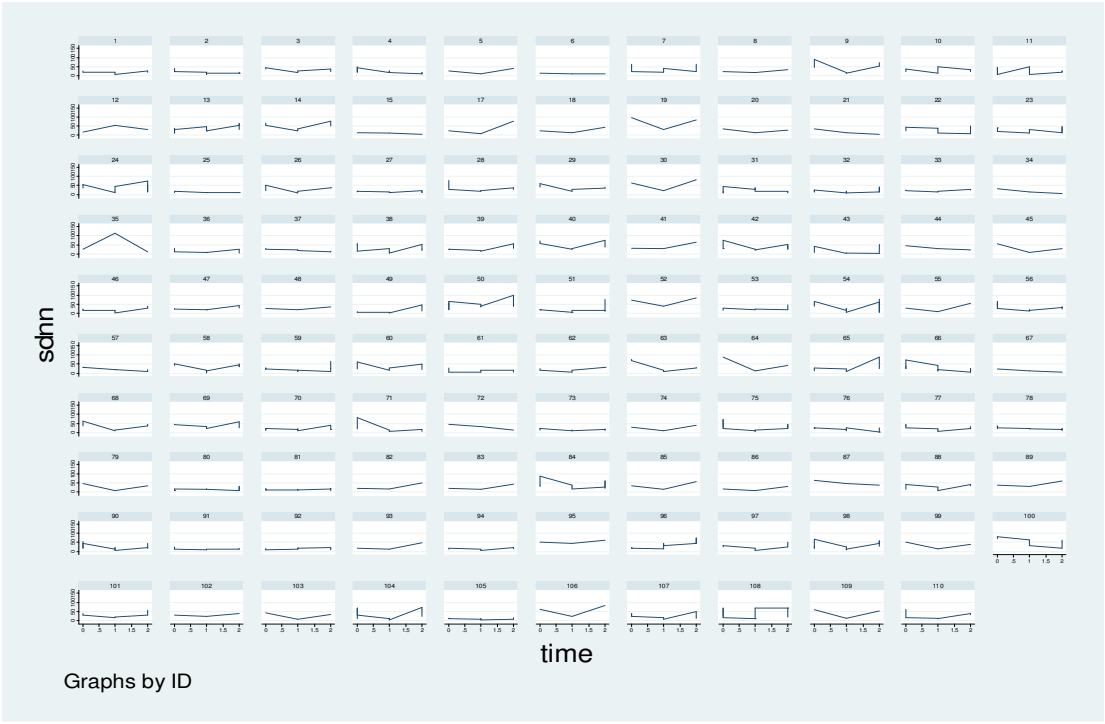


Individual mean heart rate plots over time during subclincal seizures

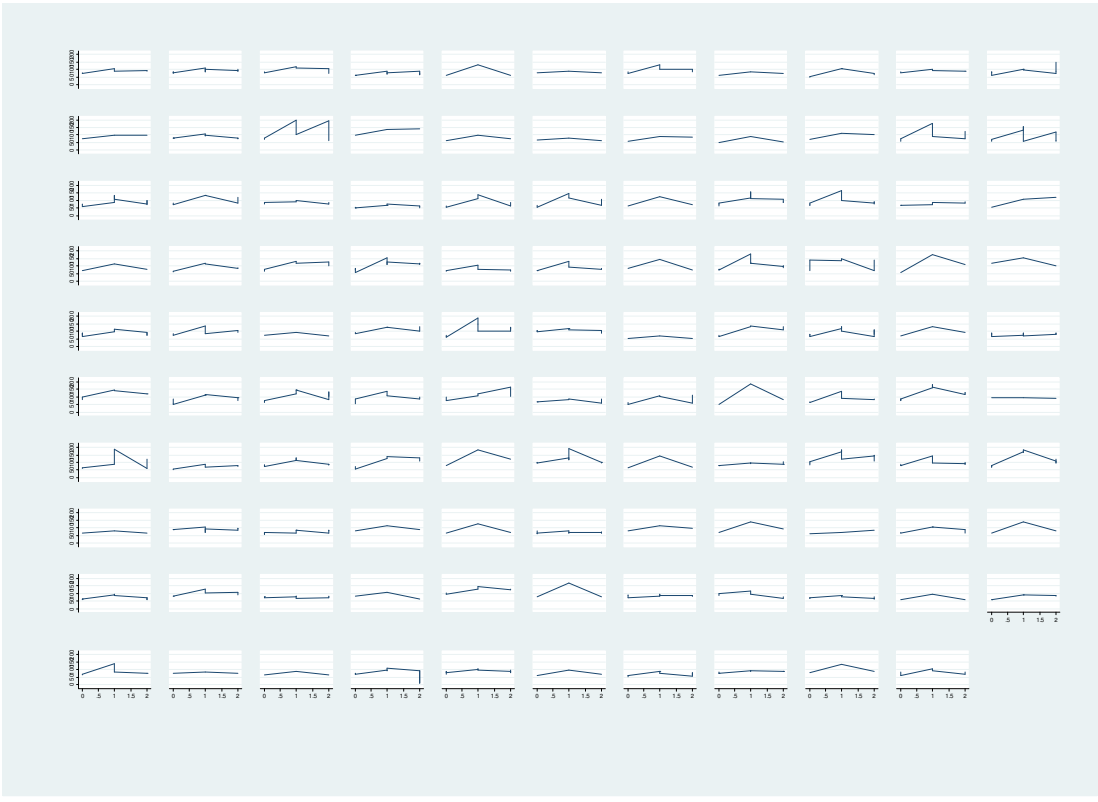


Appendix 1.4

Individual HRV plots during clinical seizures (Chapter 5)



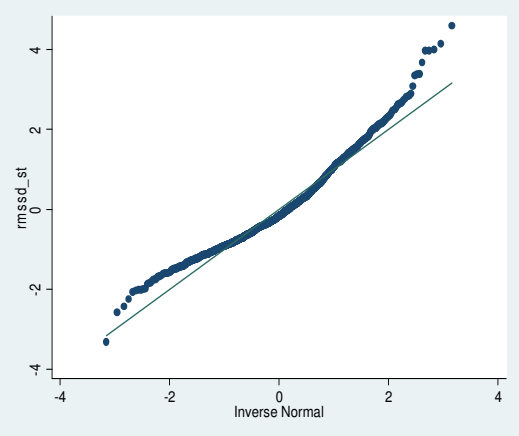
Individual mean heart rate plots during clinical seizures (Chapter 5)



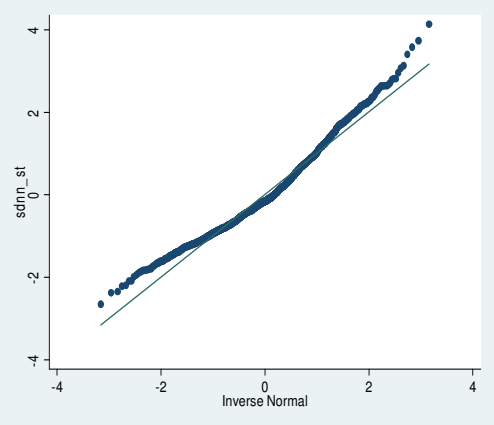
Appendix 1.5

Skewness of HRV data in chapter 6

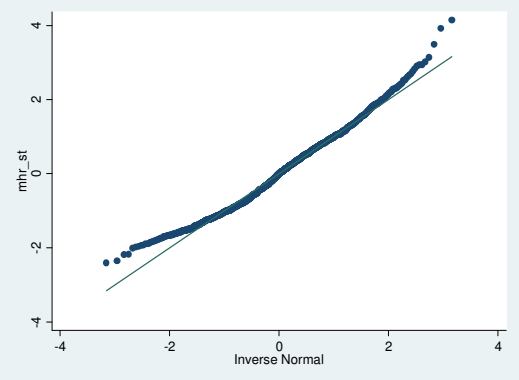
RMSSD



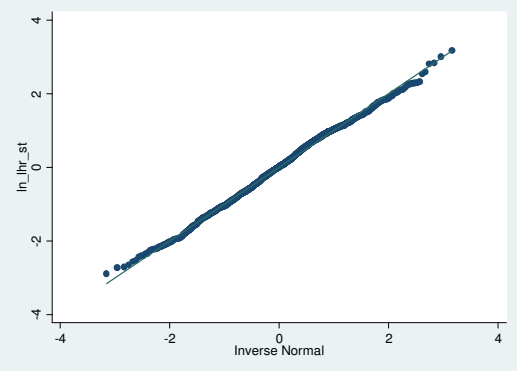
sdnn



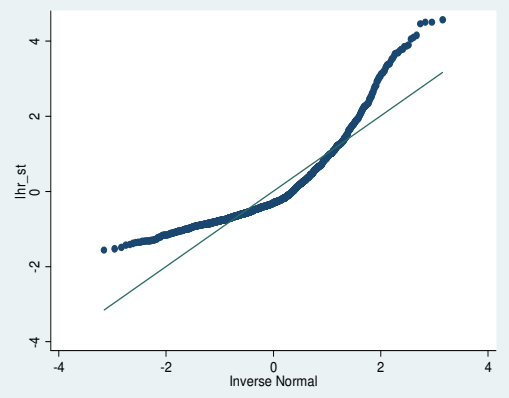
MHR



Log (LF/HF)



LF/HF

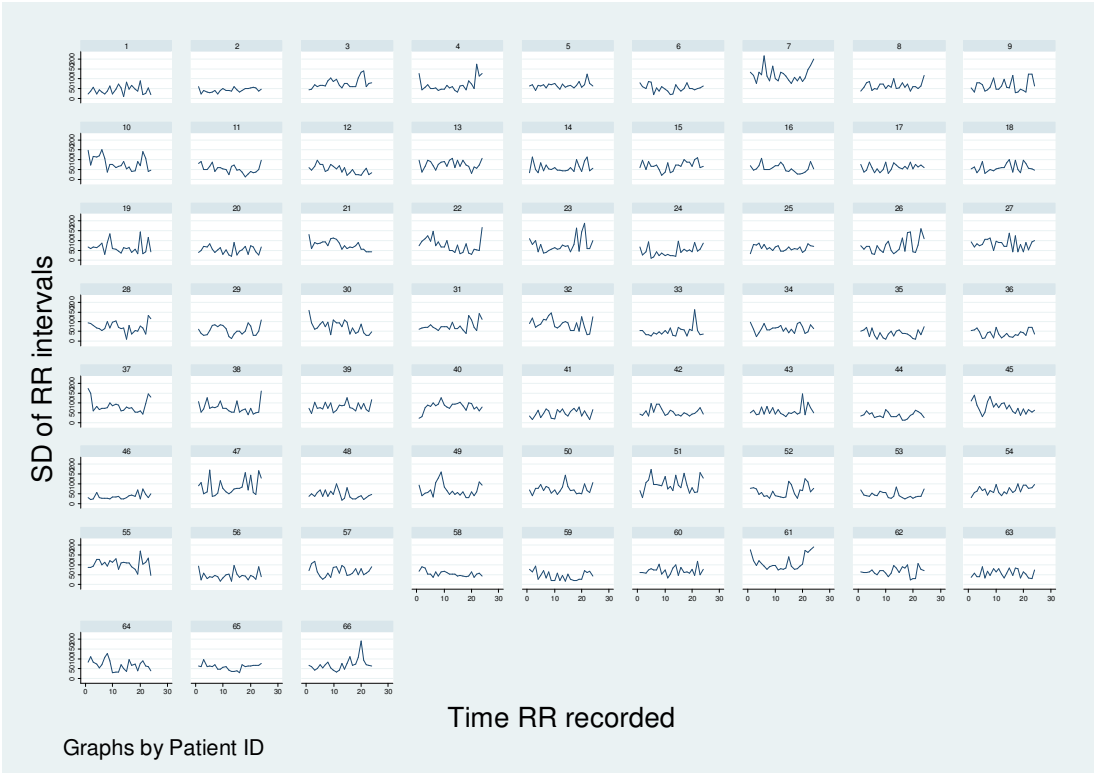


All data are normally distributed except the LF/HF ratio which was logarithmically transformed before fitting into the statistical model. [Stata command qnorm (*var*)]

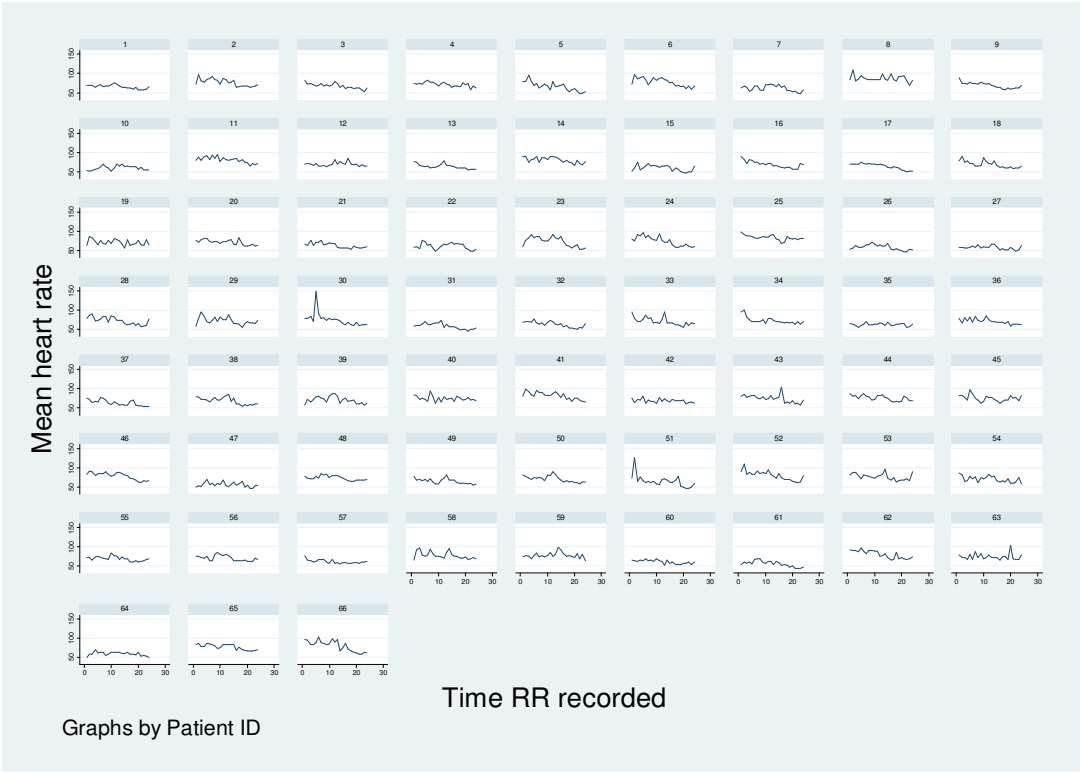
Appendix 1.6

24 hour profile plots of RMSSD in each patient

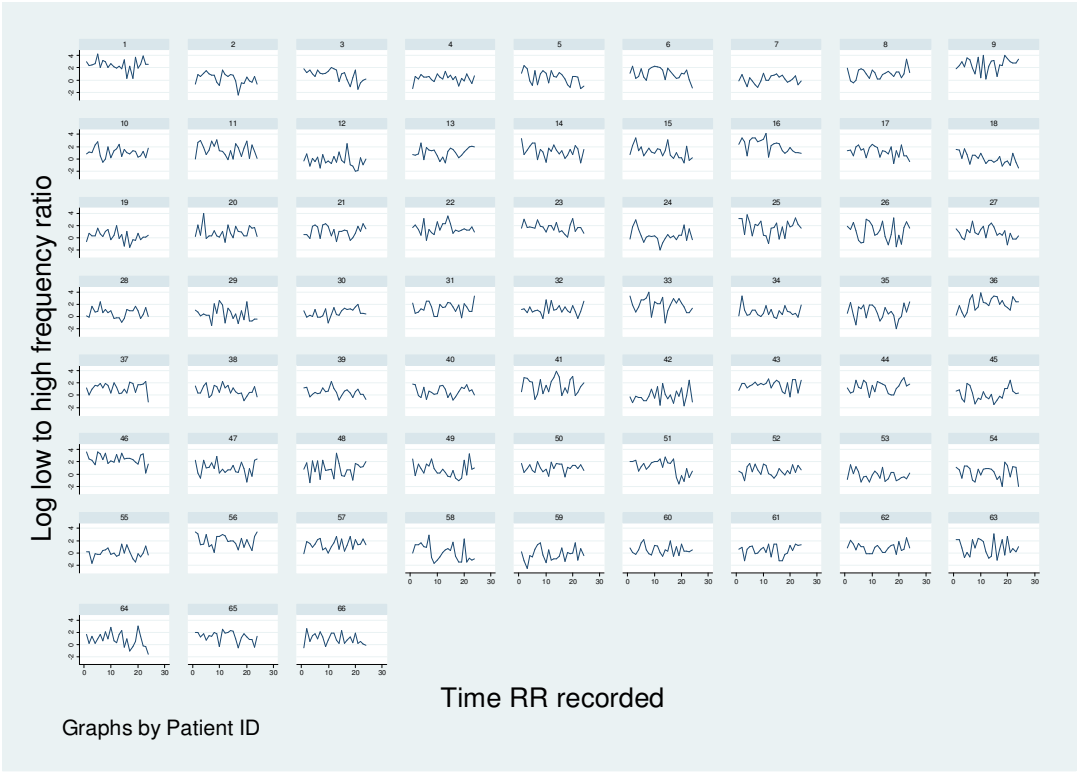
24 hour profile plots of sdnn in each patient



24 hour profile plots of mean heart rates in each patient



24 hour profile plots of Log LF/HF ratio in each patient



All the graphs beginning from left to right, starts from 8am to 7am